

EXHIBIT 6



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

11 November 2015
EMA/762033/2015
Pharmacovigilance Risk Assessment Committee (PRAC)

Assessment report

Review under Article 20 of Regulation (EC) No 726/2004

Human papillomavirus (HPV) vaccines

Procedure numbers:

Cervarix: EMEA/H/A20/1421/C/0721/0071

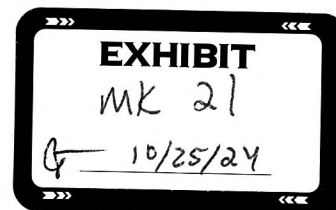
Gardasil: EMEA/H/A20/1421/C/0703/0060

Gardasil 9: EMEA/H/A20/1421/C/3852/0001

Silgard: EMEA/H/A20/1421/C/0732/0054

Note

Assessment report as adopted by the PRAC and taken into account by the CHMP in its opinion with all information of a commercially confidential nature deleted.



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1. Background information on the procedure

Human papillomavirus (HPV) vaccines have been authorised in the European Union since 2006 for the prevention of premalignant genital lesions (cervical, vulvar and vaginal), and cervical cancers caused by HPV infection. Gardasil, Silgard and Gardasil 9 are additionally indicated for prevention of premalignant anal lesions, and anal cancers and genital warts (*condyloma acuminata*) causally related to specific HPV types. Following approval, these vaccines have been introduced in national immunisation programs worldwide, including in most EU Member States.

The efficacy and safety of the HPV vaccines have been evaluated in large clinical studies and the benefit of these vaccines in protecting against HPV related diseases is well established. Every year, 34,000 women in Europe are diagnosed with cervical cancer, and 13,000 of them die. The use of HPV vaccines are expected to eventually prevent a large proportion of these cases.

Since launch, more than 63 million subjects are estimated to have been vaccinated with Gardasil worldwide. Cumulative marketing exposure to Cervarix is estimated as being more than 19 million subjects worldwide.

Routine surveillance of suspected adverse reaction reports has raised questions on the potential association between the use of the vaccines and two syndromes in particular, which are known as Complex regional pain syndrome (CRPS) and Postural orthostatic tachycardia syndrome (POTS). The majority of the reported cases do not have a well-defined diagnosis. These syndromes have been reviewed repeatedly since 2013 by the PRAC within routine safety follow-up procedures, and a relationship with HPV vaccines has not been concluded in these previous procedures.

Individual case reports and case series of CRPS and POTS suspected to be linked to a HPV vaccine have been published in the literature from several geographically distinct locations. Literature reports of CRPS come from Australia, Germany and Japan and reports of POTS originate from USA, Japan and Denmark.

These syndromes have been known for a long time before the introduction of the HPV vaccines. It is recognised that these syndromes can occur in the general non-vaccinated population and it was therefore important to undertake further review to determine whether the number of cases reported with the HPV vaccines is greater than would ordinarily be expected in the absence of vaccination and whether the currently available data supports a causal association with HPV vaccines.

The majority of POTS cases that have been reported come from one clinic in Denmark. Furthermore, there has been great media attention regarding potential adverse reactions associated with the HPV vaccine, and concerns regarding the safety of these vaccines have been raised. Therefore, Denmark asked the European Commission to initiate another in depth review.

On 09 July 2015 the European Commission (EC) triggered a procedure under Article 20 of Regulation (EC) No 726/2004 resulting from pharmacovigilance data. The EC requested the Agency to give its opinion on whether there is evidence of a causal association between HPV vaccines and CRPS and/or POTS, and if available information may require updates to the advice to healthcare professionals and patients, including changes to product information or other regulatory measures on the marketing authorisations concerned.

2. Scientific discussion

2.1. Introduction

HPV infection

HPV infection causes benign and malignant dysplastic disease in both men and women, localized primarily in the anogenital area and aerodigestive tract. Persistent HPV infection significantly increases the risk of cervical and other anogenital cancers, and oropharyngeal cancers. Overall, HPV is responsible for approximately 5% of the global cancer disease burden.

Cervical Cancer and Precancerous Dysplasia. Nearly 100% of cervical cancers are caused by HPV infection. Cervical cancer is the second most common cancer in women worldwide, with approximately 530,000 new cases diagnosed each year and 275,000 deaths annually. In the European Union, about 34,000 new cervical cancer cases are diagnosed every year causing about 13,000 deaths per year.

Non-Cervical HPV Disease. Infection with HPV is also associated with anal, vulvar, vaginal, penile, and oropharyngeal cancers. Each of the HPV-related diseases is much less frequent than cervical cancer, but taken together, they represent a significant human health and economic burden. Of particular concern, the incidence of anal cancer has been increasing in both men and women over the past several decades. In Europe, for example, approximately 90% of anal cancers, 15% of vulvar cancers, 70% of vaginal cancers, and 30 to 40% of penile cancers are estimated to be caused by HPV infection; about 16,000 new non-cervical HPV-related anogenital cancer cases are diagnosed in men and women every year in Europe.

The incidence of HPV-associated oropharyngeal cancer is also increasing and approximately 8,100 new HPV-related oropharyngeal cancer cases are estimated to be diagnosed every year in Europe.

Benign HPV Disease. Infection with HPV also causes benign lesions like *condyloma acuminata* (anogenital warts) located in the genital or perianal region and juvenile recurrent respiratory papillomatosis (RRP) primarily located in the larynx. RRP is rare but can be life-threatening and is thought to occur by transmission of the virus from an infected mother to her child. Treatment of these lesions is often lengthy and painful, and RRP often has high recurrence rate. In Europe, the incidence rate of anogenital warts is estimated to vary between 150 and 170 per 100,000 person-year in the general population, and is generally found to be highest among 20-24 years old individuals.

Complex regional pain syndrome (CRPS)

Complex regional pain syndrome (CRPS) is a debilitating, painful condition in a limb, associated with sensory, vasomotor, sudomotor, motor and dystrophic changes after injury to that limb. The events that precipitate CRPS are most commonly some sort of trauma, such as fractures, sprains, and surgery, but may also include injections, local infections, burns, frostbites, even pregnancy, as well as stroke or myocardial infarction. However, the exact nature and combination of CRPS symptoms and their severity are not related to the severity of precipitating trauma, and more than 10% of patients may not even recall any precipitating event. CRPS can be divided into two types based on the absence (CRPS-1, much more common) or presence (CRPS-2) of a lesion to a major nerve.

CRPS usually affects one limb, but in a small proportion of cases may later spread to additional limbs. Pain is typically the predominant symptom of CRPS, often associated with limb dysfunction and psychological distress.

The diagnosis of CRPS is based on clinical examination and is given when patients meet certain diagnostic criteria (Harden et al, 2007¹ and 2010)². There are no specific imaging or laboratory tests for CRPS. An international consensus group has agreed on criteria for CRPS (the 'Budapest' criteria, table 1). These criteria were developed by using approved and codified, empirically validated, statistically derived revisions of the International Association for the Study of Pain (IASP) criteria for CRPS.

The 'Budapest' criteria are summarised in the table 1 below.

Table 1. - The 'Budapest' criteria for CRPS

1. Continuing pain which is disproportionate to any inciting event.

2. Must report at least one symptom in 3 of the 4 following categories:

CATEGORY	Symptoms
Sensory:	Reports of hyperaesthesia and/or allodynia
Vasomotor:	Reports of temperature asymmetry and/or skin color changes and/or skin color asymmetry
Sudomotor/ edema:	Reports of edema and/or sweating changes and/or sweating asymmetry
Motor/trophic:	Reports of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and /or trophic changes (hair, nail, skin)

3. Must display at least one sign at time of evaluation in 2 or more of the following categories:

CATEGORY	Signs
Sensory:	Evidence of hyperalgesia and/or allodynia
Vasomotor:	Evidence of temperature asymmetry and/or skin color changes and/or asymmetry
Sudomotor/ edema:	Evidence of edema and/or sweating changes and/or sweating asymmetry
Motor/trophic:	Evidence of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and /or trophic changes (hair, nail, skin)

4. There is no other diagnosis that better explains the signs and symptoms.

The onset of symptoms in the majority of cases occurs within one month of the trauma or immobilisation of the limb. There is no proven cure for CRPS. Prompt diagnosis and early treatment are considered best practice in order to avoid secondary physical problems associated with disuse of the affected limb and the psychological consequences of living with undiagnosed chronic pain.

Since the condition is infrequent, and the range of symptoms can mimic a large number of other possible conditions seen by practitioners from various professional backgrounds, patients commonly experience a delay in diagnosis and the start of appropriate therapies. It is generally expected that these patients are referred to pain specialists for adequate assessment and tailored treatment

Two population-based studies^{3,4} of outcome in CRPS have been published. One suggested that 74% of patients experienced resolution of the syndrome, with symptoms lasting a median of 7 months. Another suggested that only 30% of CRPS patients considered themselves recovered, 16% still suffered from severe progressive disease, and the remainder was stable an average of 5.8 years after onset.

¹ Harden et al, (2007), Proposed new diagnostic criteria for complex regional pain syndrome. Pain Med;8(4):326-31.

² Harden et al, (2010), Validation of proposed diagnostic criteria (the "Budapest Criteria") for Complex Regional Pain Syndrome. Pain. Aug;150(2):268-74

³ Sandroni et al, (2003) Complex regional pain syndrome type I: incidence and prevalence in Olmsted county, a population-based study. Pain;103(1-2):199-207.

⁴ de Mos et al, (2009) Outcome of the complex regional pain syndrome Clin J Pain; 25,590 - 597

A definition of recovery from CRPS has not yet been agreed. Limb signs (such as swelling, sweating and colour changes) usually reduce with time, even where pain persists. However, such reduction of limb signs is in itself not 'recovery'. Where pain persists, the syndrome is best considered to be active. Approximately 15% of sufferers will have unrelenting pain and physical impairment >5 years after CRPS onset, although more patients will have a lesser degree of ongoing pain and dysfunction impacting on their ability to work and function normally. For those in whom pain persists, psychological symptoms (anxiety, depression), and loss of sleep are likely to develop, even if they are not prominent at the outset.

Based on data by de Mos and colleagues (2007)⁵, the incidence rate of CRPS-1 in the background population is reported to be 14.9 and 28.0 per 100,000 person-years in females 10-19 years old and 20-29 years old, respectively. Corresponding rates were lower in males, reported to be 1.8 and 6.2 per 100,000 person-years in males 10-19 years old and 20-29 years old, respectively.

Overall, given the complexity of the syndrome and likely differential practice in approaches to diagnosis and management across countries and centres, reported background incidence may differ between countries.

Postural orthostatic tachycardia syndrome (POTS)

Postural orthostatic tachycardia syndrome (POTS) is characterised by an abnormally large increase in heart rate when changing from a lying down to a standing up position, without any orthostatic hypotension. In POTS, this excessive heart rate increase is usually accompanied by a range of symptoms of orthostatic intolerance. These symptoms may include palpitations, light headedness, weakness, 'brain-fog', peripheral coldness and purplish skin discolouration and blurred vision. Some sufferers also experience fainting.

Although defined and diagnosed mainly by the tachycardia and orthostatic symptoms, POTS is often associated with a wide range of other symptoms such as migraine-like headaches, chronic aches and pains, gastrointestinal symptoms (nausea, bloating, abdominal pain), sleep disturbance and shortness of breath. In particular, fatigue is a very common feature and there is now recognised to be a significant overlap between POTS and Chronic fatigue syndrome (CFS). However, there is no set pattern of symptoms in POTS sufferers and, aside from the defining symptom of tachycardia, different people will show different symptoms. This wide spectrum of symptoms probably reflects that the syndrome has several distinct pathophysiological mechanisms.

If other causes are ruled out, POTS may be diagnosed if these chronic symptoms are also associated with an excessive increase in heart rate when changing from horizontal to a standing up position. For POTS to be diagnosed, patients need to experience a sustained increase in heart rate of 30 beats per minute or more within 10 minutes of standing (or with tilt table test), without a fall in blood pressure. For those aged 12-19 years this increase should be least 40 beats per minute (Sheldon et al, 2015⁶; see table 2).

The diagnostic criteria of POTS are based on the tilt-test or active standing test (also known as Schellong test). Studies on subjects from the general population have suggested that having a positive tilt-test in an adolescent patient – regardless of symptoms – is common (Singer et al, 2012⁷, Zhao et

⁵ de Mos et al, (2007) The incidence of complex regional pain syndrome: A population-based study, *Pain*; 129, 12-20.

⁶ Sheldon et al, (2015) 2015 heart rhythm society expert consensus statement on the diagnosis and treatment of postural tachycardia syndrome, inappropriate sinus tachycardia, and vasovagal syncope. *Heart Rhythm* 12(6): e41-63.

⁷ Singer et al, (2012). Postural tachycardia in children: what is normal? *Journal of Pediatrics*; 160:222-226.

al, 2015⁸). A diagnosis of POTS requires that other symptoms – such as light-headedness, dizziness, or fatigue – are present as well. A definition of a syndrome that combines unspecific symptoms with a diagnostic test that is frequently positive in the normal population underlines the difficulties of studying such a syndrome and trying to establish reliable incidence estimates. This also underlines the necessity to exclude other conditions before a diagnosis of POTS is made.

In many people diagnosed with POTS, the range of symptoms can have a detrimental impact on the overall quality of life. Anxiety, depression, and other psychiatric disorders can also add to the complexity of the syndrome.

Table 2. - Definition of cases for POTS (based on Raj SR, 2013⁹ and Sheldon et al, 2015)

Case definition based on Raj 2013 and Sheldon 2015 Publications
<p>Postural tachycardia syndrome (POTS) is defined as a clinical syndrome that is usually characterized by</p> <p>(1) frequent symptoms that occur with standing such as light headedness, palpitations, tremulousness, generalized weakness, blurred vision, exercise intolerance, and fatigue which improve with recumbence</p> <p>(2) an increase in heart rate of ≥ 30 bpm when moving from a recumbent to a standing position held for more than 30 seconds (or ≥ 40 bpm in individuals 12 to 19 years of age) in the absence of orthostatic hypotension (>20 mmHg drop in systolic blood pressure)</p> <p>(3) Symptoms last > 6 months</p> <p>(4) Absence of other overt cause of orthostatic symptoms or tachycardia (e.g., active bleeding, acute dehydration, medications)</p>

POTS can affect people of all ages, but the overwhelming majority of patients are women (80% to 85%) of child-bearing age (13–50 years). In adolescence, the majority of affected individuals report symptoms beginning within a year or two of the beginning of puberty, with worsening symptoms until the age of 16. About 80% of female patients report an exacerbation of symptoms around menstruation (Raj SR, 2013). It is estimated that at least 150 girls and young women per million may develop POTS each year. Although POTS is thought to be under-diagnosed, there is a gradually increasing awareness of POTS and diagnoses may be increasing.

A recent review by Kizilbash and colleagues (2014)¹⁰ summarises what is currently known about POTS in adolescence. Whilst each patient has a unique set of symptoms, it is said that their stories often sound familiar. Parents and adolescent patients with POTS often describe the long and difficult process they experience from the moment they became ill, to decreased school attendance with dropped extracurricular activities and poor academic performance, to visiting a variety of doctors in order to find answers about their child's illness. In this process, they often receive different diagnoses. According to Kizilbash and colleagues (2014) there are several typical features retrospectively identified in many adolescent POTS patients at presentation, including symptom onset during early puberty, high achievers in school and athletics, joint hypermobility, and recent illness or injury. Many adolescents with POTS have hyper-extensibility, and some are thought to have "benign joint hypermobility syndrome". It is not clear whether the elastic soft tissues actually predispose to the development of POTS or if the lax tissues simply allow further increases in vasodilatation that make it

⁸ Zhao et al, (2015) A cross-sectional study on upright hear rate and BP changing characteristics: basic data for establishing diagnosis of postural orthostatic tachycardia syndrome and orthostatic hypertension. BMJ Open; 5:e007356.

⁹ Raj SR, (2013) Postural tachycardia syndrome (POTS). Circulation. Jun 11;127(23):2336-42.

¹⁰ Kizilbash et al, (2014) Adolescent fatigue, POTS, and recovery: A guide for clinicians. Current Problems in Pediatric and Adolescent Health Care. 44; 5, 108–133

more likely for hyper-extensible individuals to report more venous pooling and dizziness when they get POTS.

Patients frequently report that their symptoms began after acute stressors such as pregnancy, major surgery, or a presumed viral illness, but in others cases, symptoms develop more insidiously (Raj SR, 2013). A large number of patients initially become symptomatic following a significant febrile illness, often mononucleosis or influenza (Kizilbash et al, 2014).

The causes and pathophysiology of POTS are not well understood, and there is no single precipitating factor. Although a decrease in return of blood to the heart generally underlies the symptoms of POTS, the causes of this likely involve multiple abnormal or excessive physiological processes that differ between sufferers. This is why POTS is classed as a syndrome, rather than a specific disease.

Many sufferers experience full recovery over time with or without treatment, but some have persistent symptoms. About 50% of patients with post-viral POTS will have partial or complete recovery within two to five years. Prognosis is generally better in younger people. Ninety per cent of patients will respond to a combination of physical and pharmacotherapy (Grubb et al, 2006)¹¹. Occasionally, some patients experience deterioration in their daily life activity over time to such an extent that they are unable to continue normal employment or educational activities.

Overlap of POTS with Chronic fatigue syndrome (CFS)

Many patients diagnosed with Chronic fatigue syndrome (CFS, also known as myalgic encephalomyelitis or ME) also show symptoms of orthostatic intolerance and signs of autonomic dysfunction. Several studies have shown that POTS can also be diagnosed in those with CFS, ranging from 13% (Lewis et al, 2013)¹² to 27% (Hoad et al, 2008)¹³. Some studies in the US suggest the proportion of CFS patients with POTS is even higher. The level of overlap will likely depend on the selection criteria within each study, and it is unclear how these estimates can be generalised. Donegan and colleagues (2013)¹⁴ provided an estimated background incidence rate of CFS among adolescent girls of 30-70 per 100,000 person-years in the UK and Bakken and colleagues (2014)¹⁵ provided an estimate of 70 per 100,000 person-years in Norway.

It is currently unclear whether POTS is a separate clinical entity distinct from CFS, or whether patients with POTS form a subset of those with CFS with a specific group of particularly marked symptoms (Lewis et al, 2013). As chronic fatigue is a common presenting feature in POTS, CFS may often be diagnosed initially (or co-diagnosed) particularly in adolescents. With increasing recognition of POTS in a subset of CFS patients, POTS may be a differential diagnosis in many who are under evaluation for CFS. According to MacDonald and colleagues (2014)¹⁶, it is becoming increasingly clear that, historically, many patients with POTS were given a diagnosis of CFS.

¹¹ Grubb et al, (2006) The postural tachycardia syndrome: A concise guide to diagnosis and management. Journal Cardiovascular Electrophysiology 17: 108-112

¹² Lewis et al, (2013) Clinical characteristics of a novel subgroup of chronic fatigue syndrome patients with postural orthostatic tachycardia syndrome. J.Int Med; 273, 5, 501-510

¹³ Hoad et al, (2008) Postural orthostatic tachycardia syndrome is an under-recognized condition in chronic fatigue syndrome. Q J Med. 101, 961-965.

¹⁴ Donegan et al, (2013) Bivalent human papillomavirus vaccine and the risk of fatigue syndromes in girls in the UK. Vaccine; 31(43): 4961-7

¹⁵ Bakken et al, (2014) Two age peaks in the incidence of chronic fatigue syndrome/myalgic encephalomyelitis: A population based registry study from Norway, BMC Medicine, 12:167

¹⁶ MacDonald et al, (2014) Postural tachycardia syndrome is associated with significant symptoms and functional impairment predominantly affecting young women: a UK perspective. BMJ Open;4:e004127

Medicinal products involved in this review

HPV vaccines have been authorised in the European Union since 2006. Following approval, these vaccines have been introduced in national immunisation programs worldwide, including in most EU Member States.

Cervarix

Cervarix (Bivalent HPV vaccine (types 16, 18)) is a non-infectious recombinant vaccine prepared from the highly purified virus-like particles (VLPs) of the major capsid L1 protein of oncogenic HPV types 16 and 18. This vaccine is adjuvanted with AS04 (composed of aluminium hydroxide and 3-O-desacyl-4'-monophosphoryl lipid A (MPL)).

HPV 16 and HPV 18 are estimated to be responsible for approximately 70% of cervical cancers and 75-80% of anal cancers; 80% of adenocarcinoma in situ (AIS); 45-70% of high-grade cervical intraepithelial neoplasia (CIN 2/3); 25% of low grade cervical intraepithelial neoplasia (CIN 1); approximately 70% of HPV related high-grade vulvar (VIN 2/3) and vaginal (VaIN 2/3) intraepithelial neoplasia and 80% of HPV related high-grade anal (AIN 2/3) intraepithelial neoplasia.

Cervarix is indicated in females from 9 years of age onwards for the prevention of persistent infection, premalignant genital (cervical, vulvar and vaginal) lesions and cervical, vulvar and vaginal cancers (squamous-cell carcinoma and adenocarcinoma) caused by oncogenic HPV.

The age at which people receive the vaccine, e.g. in the context of a national vaccination programme, can vary between countries depending on their official recommendations. The vaccination schedule depends on the age of the subject:

- From 9 up to and including 14 years of age: 2 doses each of 0.5 ml. The second dose given between 5 and 13 months after the first dose¹⁷; or 3 doses each of 0.5 ml at 0, 1, 6 months¹⁸
- From 15 years of age and above: 3 doses each of 0.5 ml at 0, 1, 6 months[†]

Although the necessity for a booster dose has not been established, an anamnestic response has been observed after the administration of a challenge dose.

Cervarix is for intramuscular injection in the deltoid region.

The efficacy of Cervarix was assessed in two controlled, double-blind, randomised Phase II and III clinical trials that included a total of 19,778 women aged 15 to 25 years.

The phase III trial (study 008) enrolled women without pre-screening for the presence of HPV infection, i.e. regardless of baseline cytology and HPV serological and DNA status. The primary efficacy endpoint was CIN2+ associated with HPV-16 and/or HPV-18 (HPV-16/18). Cervical Intraepithelial Neoplasia (CIN) grade 2 and 3 (CIN2/3) and cervical adenocarcinoma in situ (AIS) were used in the clinical trials as surrogate markers for cervical cancer. The secondary endpoints included 6- and 12-month persistent infection. The primary analyses of efficacy were performed on the According to Protocol cohort (ATP cohort: including women who received 3 vaccine doses and were DNA negative and seronegative at month 0 and DNA negative at month 6 for the HPV type considered in the analysis) This cohort included women with normal or low-grade cytology at baseline and excluded only women with high-grade cytology (0.5% of the total population).

¹⁷ If the second vaccine dose is administered before the 5th month after the first dose, a third dose should always be administered

¹⁸ If flexibility in the vaccination schedule is necessary, the second dose can be administered between 1 month and 2.5 months after the first dose and the third dose between 5 and 12 months after the first dose

Vaccine efficacy against the primary endpoint CIN2+ at the end of study was 94.9% (95% CI 87.7; 98.4) against CIN2+ and 91.7% (95% CI 66.6;99.1) against CIN 3+ related to HPV 16/18. Vaccine efficacy against virological endpoints (6-month and 12-month persistent infection) associated with HPV-16/18 observed in the ATP cohort at the end of study was 94.3% (95% CI 92.0; 96.1) against 6-month persistent infection and 92.9% (95% CI 89.4; 95.4) against 12-month persistent infection.

In a pooled analysis, 99.7% and 100% of females aged 9 years seroconverted to HPV types 16 and 18, respectively after the third dose (at month 7) with GMTs at least 1.4-fold and 2.4-fold higher as compared to females aged 10-14 years and 15 to 25 years, respectively.

In two clinical trials (HPV-012 & -013) performed in girls aged 10 to 14 years, all subjects seroconverted to both HPV types 16 and 18 after the third dose (at month 7) with GMTs at least 2-fold higher as compared to women aged 15 to 25 years.

In clinical trials (HPV-070 and HPV-048) performed in girls aged 9 to 14 years receiving a 2-dose schedule (0, 6 months or 0, 12 months) and young women aged 15-25 years receiving Cervarix according to the standard 0, 1, 6 months schedule, all subjects seroconverted to both HPV types 16 and 18 one month after the second dose. The immune response after 2 doses in females aged 9 to 14 years was non-inferior to the response after 3 doses in women aged 15 to 25 years.

On the basis of these immunogenicity data, the efficacy of Cervarix is inferred from 9 to 14 years of age.

Cervarix was first authorised in Australia in May 2007 and has been authorised in Europe since September 2007. It is currently approved in 135 countries worldwide.

At the data lock point (15 June 2015) used for this analysis, a total of 57,094,396 doses have been distributed worldwide, and the number of subjects exposed to at least one dose of Cervarix can be estimated to be to 19 million.

Gardasil/Silgard

Gardasil and Silgard are two different marketing authorisations for the same adjuvanted non-infectious recombinant quadrivalent vaccines (qHPV) prepared from the highly purified virus-like particles (VLPs) of the major capsid L1 protein of HPV types 6, 11, 16 and 18. The vaccine is adjuvanted with amorphous aluminium hydroxyphosphate sulphate.

HPV types 16 and 18 are described above. HPV 6 and 11 are responsible for approximately 90% of genital warts and 10% of low grade cervical intraepithelial neoplasia (CIN 1). CIN 3 and AIS have been accepted as immediate precursors of invasive cervical cancer.

Gardasil/Silgard are indicated for use from the age of 9 years of age for the prevention of:

- premalignant genital lesions (cervical, vulvar and vaginal), premalignant anal lesions, cervical cancers and anal cancers causally related to certain oncogenic HPV types
- genital warts (*condyloma acuminata*) causally related to specific HPV types.

The efficacy of Gardasil was assessed in 16- through 26- year-old women in 4 placebo-controlled, double-blind, randomized Phase II and III clinical studies including a total of 20,541 women, who were enrolled and vaccinated without pre-screening for the presence of HPV infection. The primary analyses of efficacy, with respect to vaccine HPV types (HPV 6, 11, 16, and 18), were conducted in the per-protocol efficacy (PPE) population (i.e. all 3 vaccinations within 1 year of enrolment, no major protocol

deviations and naïve to the relevant HPV type(s) prior to dose 1 and through 1 month after dose 3 (Month 7)).

The primary efficacy endpoints included HPV 6-, 11-, 16-, or 18-related vulvar and vaginal lesions (genital warts, VIN, VaIN) and CIN of any grade and cervical cancers (Protocol 013, FUTURE I), HPV 16- or 18-related CIN 2/3 and AIS and cervical cancers (Protocol 015, FUTURE II), HPV 6-, 11-, 16-, or 18-related persistent infection and disease (Protocol 007), and HPV 16-related persistent infection (Protocol 005).

At end of study and in the combined protocol analysis, the efficacy of Gardasil against HPV 6-, 11-, 16-, 18-related CIN 1 was 95.9 % (95% CI: 91.4, 98.4), the efficacy of Gardasil against HPV 6-, 11-, 16-, 18-related CIN (1, 2, 3) or AIS was 96.0% (95% CI: 92.3, 98.2), the efficacy of Gardasil against HPV 6-, 11-, 16-, 18-related VIN2/3 and VaIN 2/3 was 100% (95% CI: 67.2, 100) and 100% (95% CI: 55.4, 100), respectively. The efficacy of Gardasil against HPV 6-, 11-, 16-, 18-related genital warts was 99.0% (95% CI: 96.2, 99.9).

The protective effect has been statistically significant for up to 6 years following vaccination, and immune responses remain on a plateau level for at least 8 years. The exact duration of protection has not yet been determined.

The quadrivalent human papillomavirus (qHPV) vaccine has been authorised in the EU for prevention of cervical and various other cancers caused by HPV infection since 2006. Worldwide 190,897,611 doses of qHPV vaccine have been distributed until 31 May 2015, corresponding to more than 63 million individuals exposed (assuming 3 doses per individual).

Gardasil 9

Gardasil 9 is an adjuvanted non-infectious recombinant 9-valent vaccine. It is prepared from the highly purified virus-like particles (VLPs) of the major capsid L1 protein from the same four HPV types (6, 11, 16, 18) in qHPV vaccine Gardasil/Silgard and from 5 additional HPV types (31, 33, 45, 52, 58). It uses the same amorphous aluminium hydroxyphosphate sulphate adjuvant as the qHPV vaccine.

Based on epidemiology studies, Gardasil 9 is anticipated to protect against the HPV types that cause approximately: 90% of cervical cancers, more than 95% of adenocarcinoma in situ (AIS), 75-85% of high-grade cervical intraepithelial neoplasia (CIN 2/3), 85-90% of HPV related vulvar cancers, 90-95% of HPV related high-grade vulvar intraepithelial neoplasia (VIN 2/3), 80-85% of HPV related vaginal cancers, 75-85% of HPV related high-grade vaginal intraepithelial neoplasia (VaIN 2/3), 90-95% of HPV related anal cancer, 85-90% of HPV related high-grade anal intraepithelial neoplasia (AIN2/3), and 90% of genital warts.

Gardasil 9 is indicated for active immunisation of individuals from the age of 9 years of age against the following HPV diseases:

- Premalignant lesions and cancers affecting the cervix, vulva, vagina and anus caused by vaccine HPV types
- Genital warts (*Condyloma acuminata*) caused by specific HPV types.

Efficacy and/or immunogenicity of Gardasil 9 were assessed in seven clinical studies. Clinical studies evaluating the efficacy of Gardasil 9 against placebo were not acceptable because HPV vaccination is recommended and implemented in many countries for protection against HPV infection and disease.

Therefore, the pivotal clinical study (Protocol 001) evaluated the efficacy of Gardasil 9 using qHPV vaccine as a comparator.

Efficacy against HPV Types 6, 11, 16, and 18 was primarily assessed using a bridging strategy that demonstrated comparable immunogenicity. Immune responses, measured by GMT, for Gardasil 9 were non-inferior to immune responses for Gardasil. In clinical studies 99.6% to 100% who received Gardasil 9 became seropositive for antibodies against all 9 vaccine types by Month 7 across all groups tested.

In the pivotal study the efficacy of Gardasil 9 against HPV Types 31, 33, 45, 52, and 58 was evaluated compared to qHPV vaccine in women 16 through 26 years of age (N=14,204: 7,099 receiving Gardasil 9; 7,105 receiving qHPV vaccine). The primary efficacy analysis was performed in the per protocol efficacy (PPE) population (individuals who received all 3 vaccinations within one year of enrolment, did not have major deviations from the study protocol, were naïve (PCR negative and seronegative) to the relevant HPV type(s) (Types 31, 33, 45, 52, and 58) prior to dose 1, and who remained PCR negative to the relevant HPV type(s) through one month postdose 3 (Month 7)). Gardasil 9 was efficacious in preventing HPV 31-, 33-, 45-, 52-, and 58-related persistent infection (96.0 – 96.7%, CI 94.6 – 97.9) and disease (97.4%, CI 85.0 – 99.9). Gardasil 9 also reduced the incidence of HPV 31-, 33-, 45-, 52-, and 58-related Pap test abnormalities, cervical and external genital procedures (92.9%, CI 90.2 – 95.1), and cervical definitive therapy procedures (90.2%, CI 75.0 – 96.8).

As for Gardasil and Cervarix, protection in younger subjects, 9-15 years, was inferred through immunological bridging.

Gardasil 9 was granted a marketing authorisation in the EU on 10 June 2015. The exposure within clinical trials corresponded to 15,800 subjects. As it is newly authorised, exposure outside of clinical trials to date is expected to be very low compared to exposure to Gardasil.

2.2. Data on safety

At the start of the referral the marketing authorisation holders (MAHs) were asked to provide cumulative reviews of available data from clinical trials, post-marketing surveillance, and literature in order to evaluate the cases of CRPS and POTS reported with their product. This was in response to a list of questions agreed by the PRAC at its meeting on 9 July 2015. Review and case detection methods should be clearly described, and MAHs were asked to provide in depth reviews of all identified reports, and discuss whether they fulfil published or recognised diagnostic criteria.

To identify potential cases of CRPS and POTS, the marketing authorisation holders (MAHs) were requested by the PRAC to search for reports specifically containing the terms POTS and CRPS. In order to identify possible cases of undiagnosed CRPS and POTS, PRAC also requested the MAHs to use common search strategies, which also used an algorithm to identify reports with combinations of signs and symptoms common in CRPS or POTS. The clinical details of all reports were individually evaluated by the MAHs to determine if the established criteria (see above section 2.1) of CRPS and POTS were fulfilled. A report was considered to either fully meet the diagnostic criteria, partially meet the diagnostic criteria or not to meet the diagnostic criteria. The MAHs were also asked to provide analyses of 'Observed versus expected' (O/E) number of reports. These analyses compared the number of reported cases (observed) with the number that would be expected to have occurred naturally in the target population, taking into account a wide range of scenarios regarding underreporting and also including reports that did not fully meet the diagnostic criteria for the respective syndrome.

Observed versus expected (O/E) analyses cannot determine causality, but they are useful in signal validation and, in the absence of robust epidemiological data, in preliminary signal evaluation¹⁹. Given uncertainties around the 'observed' number of cases, the levels of diagnostic certainty, the level of vaccine exposure and the background incidence rates, sensitivity analyses are usually applied in statistical analyses around assumed levels of under-reporting, numbers of 'confirmed' and 'non-confirmed' cases (using several categories of diagnostic certainty as appropriate), numbers of vaccinated individuals or vaccine doses administered and confidence intervals of incidence rates.

In addition to data provided by the MAHs, all other data available to the PRAC was considered in the review, including data from the published literature, from Eudravigilance and data provided by other parties (Member States and the public).

2.2.1. Cervarix

Clinical safety data (CRPS and POTS)

Safety data from 18 completed and unblinded studies with a comparator group (either placebo or another vaccine other than an HPV vaccine, i.e. Hepatitis B, Hepatitis A) which includes a total of 42,047 vaccinees (21,268 in HPV group and 20,779 in comparator groups) was pooled (data lock point 15 June 2015).

No serious or non-serious adverse event of CRPS or POTS were identified in clinical study data i.e. when searching for cases reported as 'CRPS' or 'POTS', or when searching for any cases that include signs and symptoms of CRPS (according to Harden et al, 2010; table 1), or POTS (according to Raj SR, 2013 and Sheldon et al, 2015; see table 2).

Post marketing safety data for CRPS

Using the above-mentioned search strategy and case definitions, since launch (17 May 2007) until 15 June 2015, 49 reports containing the specific term of CRPS, and 13 reports containing a range of CRPS symptoms (without the term CRPS) were identified. In identifying and evaluating the reports of CRPS the 'Budapest' criteria for CRPS were employed.

Of the reports containing the term of CRPS, 5 reports fulfilled the diagnostic criteria, 37 partially fulfilled the diagnostic criteria, 6 cases did not fulfil the diagnostic criteria and a further case lacked sufficient details for it to be able to be classified. Out of the 49 spontaneous case reports identified using the term CRPS, 40 originated from Japan, 8 from the UK and 1 from the Republic of Korea.

The search also identified reports which reported signs and symptoms of CRPS but CRPS itself was not reported. A total of 13 additional reports were identified, none of which fully or partially met the diagnostic criteria.

¹⁹ Guideline on good pharmacovigilance practices (GVP) Product – or Population - Specific Considerations I: Vaccines for prophylaxis against infectious diseases;
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/12/WC500157839.pdf

Table 3 - Post marketing data for Cervarix and CRPS

	Based on term "CRPS"	Based on symptom query
Total	49	13
Met case definition criteria	5	0
Partially met criteria	37	0
Criteria not met	6	13
Other*	1	0

* Reports lack sufficient detail for them to be classified

The O/E analysis for Cervarix covered a range of scenarios that included some or all of the cases spontaneously reported with term CRPS regardless of whether they met the diagnostic criteria and included a total of 49 cases.. The observed versus expected scenarios which were employed, also examined a risk period between 1 week and 2 years, reporting rates between 1-100%, and utilised distribution data to estimate exposure. The background incidence rates which were used for CRPS are 14.9-28 / 100,000 person years (estimated from literature²⁰)

The O/E analysis has suggested that the number of observed CRPS cases is low compared to those expected. The O/E analyses are generally reassuring with observed counts exceeding the expected only at low reporting rates and in individual countries, such as Japan, that have experienced significant media attention that is likely to have increased reporting rates and therefore low reporting rates would be unlikely.

Post marketing safety data for POTS

Since launch (17 May 2007) until 15 June 2015, a total of 19 reports were identified that reported the specific term 'POTS'. In identifying and evaluating diagnosis of reports of POTS the Raj SR (2013) and Sheldon and colleagues (2015) case definition was employed (table 2).

Out of these 19 cases, 5 fully met the diagnostic criteria, 13 partially met the diagnostic criteria and a further case lacked sufficient details for it to be able to be classified. A search was also conducted for reports that reported signs and symptoms of POTS to determine potential undiagnosed or unrecognised cases. As a result of this additional search, 7 reports of potential POTS were identified. One of these cases also had a MedDRA PT 'POTS' and therefore was included in the above analysis. The remaining 6 reported cases were considered not to meet the diagnostic criteria.

Table 4 - Post marketing data for Cervarix and POTS

	Based on term "POTS"	Based on symptom query
Total	19	6
Met case definition criteria	5	0
Partially met criteria	13	0
Criteria not met	0	6
Other*	1	0

* Reports lack sufficient detail for them to be classified

²⁰ de Mos et al, (2007) The incidence of complex regional pain syndrome: A population-based study, Pain; 129, 12-20.

The O/E analysis for Cervarix covered a range of scenarios that included some or all of the cases regardless of whether they met the diagnostic criteria and included a total of 19 cases. The O/E scenarios which were employed, also examined a risk period between 1 week and 2 years, reporting rates between 1-100%, and utilised distribution data to estimate exposure. The background incidences that were used for POTS were 15, 35, 60 or 140 per 100,000 person years (estimated from literature that 10-40% CFS patients have POTS and 20% POTS patients have CFS).

The analysis of O/E cases suggests that the number of observed POTS cases is low compared to those expected. The analyses are generally reassuring with observed counts exceeding the expected only at low reporting rates, with the exceptions of countries, such as Japan, that have experienced significant media attention that is likely to have increased reporting rates. Even in these situations the observed count only exceeded the expected if a risk period of 1 week was examined and was not true for longer risk periods.

2.2.2. Gardasil/Silgard/Gardasil 9

Data for these vaccines are presented together.

Clinical safety data (CRPS and POTS)

A total of 3 reports suggestive of CRPS (1 in Gardasil 9, 1 in Gardasil/Silgard and 1 in placebo) were identified in the clinical trial data base (60,594 subjects with 197,983 person-years follow-up). The case in the Gardasil 9 vaccine group had a likely onset of symptoms before vaccination. The report in the Gardasil/Silgard group was reported 736 days after vaccination, and the placebo case does not seem to fulfill the criteria for CRPS.

No cases suggestive of POTS were identified in clinical trials with Gardasil/Silgard, and two cases suggestive of POTS were identified with Gardasil 9. One Gardasil 9 case did not fulfil the criteria for POTS, and for the second case it is unclear how long had passed between vaccination and onset of symptoms (diagnosis was made 1389 days after administration of dose 3).

Overall, the incidences of CRPS and POTS observed in clinical studies were less than 1 case per 10,000 person-years in each of the Gardasil 9, Gardasil/Silgard and placebo cohorts.

Post marketing safety data for CRPS

The query of the company safety data base regarding CRPS yielded 53 unique medically confirmed reports temporally associated with the administration of qHPV vaccine. A separate query for reports that include various combinations of symptoms of CRPS yielded 37 additional reports.

A total of 90 potential cases of CRPS were identified worldwide for Gardasil/Silgard based on reports where the term CRPS was reported (n=53) or where a combination of various symptoms of CRPS were reported (n=37). In identifying and evaluating diagnosis of reports of CRPS the 'Budapest' criteria for CRPS were employed (table 1).

Of these 53 cases where the term CRPS was reported, 7 cases were classified as having fully met the CRPS criteria, 16 cases as having partially met the criteria and 30 cases as not meeting the criteria. Of the 37 cases which reported a combination of various symptoms of CRPS, 0 cases were classified as having fully met the diagnostic criteria, 6 cases as having partially met the diagnostic criteria and 31 cases are not meeting the diagnostic criteria.

Out of the 53 case reports identified using the term CRPS, 18 originated from Japan, 13 from the EU, 11 from the US and the remaining 11 from countries in the rest of the world. Out of the 37 cases which reported a combination of various symptoms of CRPS, 1 originated from Japan, 24 from the EU, 11 from the US and the remaining report from the a country in the rest of the world.

Table 5 - Post marketing data for Gardasil/Silgard for CRPS

	Based on term "CRPS"	Based on symptom query
Total	53	37
Met case definition criteria	7	0
Partially met criteria	16	6
Criteria not met	30	31

A total of 29 cases that either fully or partially met the criteria were included in the O/E analyses. The O/E scenarios which were employed, examined a risk period between 1 week and 2 years, reporting rates between 1-100%, and utilised distribution data to estimate exposure.

It is noted that the MAH did not include a conservative analysis to include all cases of CRPS, including those that do not meet the diagnostic criteria, however, it is considered that this approach would not add value and would simply have included cases that are unlikely to be CRPS. Furthermore, the number of expected cases would not have been as relevant in such analyses.

The results of the O/E analysis for Gardasil/Silgard showed that the observed counts were less than expected in most scenarios of under-reporting, case definitions and risk periods. The observed count exceeded the expected generally in scenarios that included partial criteria cases and at the lowest 1% reporting level. Only in Denmark and Japan did the observed exceed the expected for higher reporting levels (10-50% for Denmark (depending on risk period) and 10% for Japan). These higher reporting rates are plausible given the high public awareness in those countries.

Post marketing safety data for POTS

The query of the company safety data base for cases that include the term of POTS yielded a total of 83 reports of POTS reported following of Gardasil/Silgard received worldwide from first marketing to 15 June 2015. The query of the company safety data base for case reports that include various combinations of symptoms of POTS (but without specific mention of POTS) yielded 30 additional case reports. In identifying and evaluating diagnosis of reports of POTS the Raj 2013 and Sheldon 2015 case definition was employed.

Of these 83 cases where the term POTS was reported, 33 cases were classified as having fully met the POTS criteria, 10 cases as having partially met the criteria and 40 cases as not meeting the criteria. Of the 30 cases which reported a combination of various symptoms of POTS, 0 cases were classified as having fully met the diagnostic criteria, 3 cases as having partially met the diagnostic criteria and 27 cases are not meeting the diagnostic criteria

Out of the 83 case reports identified using the term POTS, 48 originated from the EU (41 from Denmark, 7 from the rest of EU), 28 from the US, 4 from Japan and the remaining 3 from countries in the rest of the world. Out of the 30 cases which reported a combination of various symptoms of POTS, 15 originated from the EU, 13 from the US and 2 from Japan.

Table 6 - Post marketing data for Gardasil/Silgard for POTS

	Based on PT "POTS"	Based on symptom query
Total	83	30
Met case definition criteria	33	0
Partially met criteria	10	3
Criteria not met	40	27

A total of 46 cases that either fully or partially met the criteria were included in the O/E analyses. The O/E scenarios which were employed, examined a risk period between 1 week and 2 years, reporting rates between 1-100%, and utilised distribution data to estimate exposure.

It is noted that the MAH did not include a conservative analysis to include all cases of POTS, including those that do not meet the diagnostic criteria, however, it is considered that this approach would not add value and would simply have included cases that are unlikely to be POTS. Furthermore, the number of expected cases would not have been as relevant in such analyses.

The results of the O/E analyses for POTS with Gardasil/Silgard showed that the observed number of cases was generally lower than expected under almost all assumptions for all regions and countries except for Denmark. The data showed that only in Denmark is the observed number of reports higher than expected for certain reporting scenarios (low reporting rates or short risk period). Considering the recent media attention in Denmark and active identification of cases it seems unlikely that any of the lower reporting rate scenarios are applicable and the pattern of time to onset in these cases appears to differ to that seen in cases from outside Denmark.

2.2.3. Literature review

Literature review for CRPS

A Japanese article (Kinoshita et al, 2014)²¹ generates the majority of CRPS cases identified in the literature. This article reports cases from one centre but mechanisms for referral/presentation to the centre are not described. Only two of the CRPS cases are described in some detail. Descriptive data relevant specifically for the CRPS cases are limited. The average interval from the first dose of the vaccine to the adverse event was overall in the study population 5.47±5.00 months, i.e. highly variable. It is, however, not clear from the methods description what measure of variability has been used, i.e. if "±5.00" represents the standard deviation, range, or something else. Individual values for time to onset are not presented. This means that it is not possible to compile a description of time to onset from the CRPS cases as presented in the literature.

The literature references describing CRPS in relation to HPV vaccines are summarized in the table below.

²¹ Kinoshita et al, (2014) Peripheral sympathetic nerve dysfunction in adolescent Japanese girls following immunization with the human papillomavirus vaccine. Intern Med; 53:2185-2200.

Table 7 - Summary of key publications reporting cases of CRPS in relation to HPV vaccines.

Study type / reference	Population / setting / exposure	Key result / authors conclusion
Case series (Richards et al, 2012) ²²	5 adolescents from Australia and UK. 4 exposed to HPV vaccine (3 qHPV)	The 4 HPV exposed had time-to-onset (TTO) of 0, 0, 0, and 4 days, respectively. Symptom resolution was seen within 5, 14, 60, and 201 days, respectively. "Intramuscular immunisation is sufficient to trigger the development of CRPS-1, rather than a particular vaccine antigen."
Case report in congress abstract (Haug et al, 2013)	1 individual exposed to qHPV	Within 24 hours severe pain, swelling, numbness, and coldness of the right arm and hand. On MRI small inflammatory focus in the right deltoids in the course of the Nervus cutaneus <i>brachialis lateralis</i> .
Case series / Kinoshita et al, 2014	15 adolescents from Japan with CRPS. 40 patients in total (7 exposed to Gardasil, 22 to Cervarix). 3 with CRPS+POTS. 1 with POTS.	15 cases with CRPS. In 2 cases (out of 3 with biopsy results) morphology showed endoneurial oedema and selective degeneration of unmyelinated fibres.
Abstract /Kinoshita et al. 2014	48 patients (from same clinic as above and largely overlapping time period). 18 fulfilling the diagnostic criteria for CRPS-1.	-
Abstract /Kinoshita et al, 2014	17 patients from an unknown time period.	-
Letter to the editor /	2 adolescents	Both patients fulfilled the fibromyalgia criteria and were

²² Richards et al, (2012) Complex regional pain syndrome following immunisation. Arch Dis Child;97(10):913-915.

Study type / reference	Population / setting / exposure	Key result / authors conclusion
Martinez-Lavin 2014 ²³	from Mexico.	considered fibromyalgia-like illness after HPV immunization.
Paper presented at meeting / Okuyama 2014	8 cases from Japan (bivalent type in 5 and qHPV in 3)	Adolescents may experience symptoms that are pathologically difficult to explain, including pain in the limbs after HPV vaccination. Based on the temporal sequence these are understood to be side effects from the vaccine. Management consists of excluding other diagnoses and combination therapy of physical exercise, counselling and pharmacotherapy.

Literature review for POTS

Few cases of POTS following vaccination with Cervarix have been published (Kinoshita et al, 2014) and those cases were included in the MAH safety data base and discussed above.

Overall the majority of cases described in the literature review in association with the vaccine are from one Danish Centre (Brinth et al, 2015). These are discussed in detail below and are also referenced in section 2.2.4.1 below.

The literature references describing POTS in relation to HPV vaccines are summarized in the table below.

Table 8 - Summary of key publications reporting cases of POTS in relation to HPV vaccines.

Study type / reference	Population / setting / exposure	Key result / authors conclusion
Case series (Blitshteyn et al, 2014) ²⁴	6 patients in the US (qHPV). Unclear referral /selection mechanism.	Symptoms 6 days to 2 months following HPV vaccination. 3 patients also experiencing NCS. 3 patients with small fibre neuropathy.
Case series (Kinoshita et al, 2014)	15 adolescents from Japan with CRPS. 40 patients in total (7 exposed to Gardasil, 22 to Cervarix). 3	4 cases of POTS. 2 cases presented in more detail, none of those strictly fulfilling POTS criteria.

²³ Martínez-Lavín, M. (2014) Fibromyalgia-like illness in 2 girls after human papillomavirus vaccination. Journal of Clinical Rheumatology, 20;7,392–393.

²⁴ Blitshteyn, S. (2014). Postural tachycardia syndrome following human papillomavirus vaccination. Eur J Neurol, 21(1): 135-139.

Study type / reference	Population / setting / exposure	Key result / authors conclusion
	with CRPS+POTS. 1 with POTS. One hospital department, unclear referral /selection mechanism.	
Brief report / Ikeda, 2014	Apparently from the same population described in Kinoshita et al 2014a above	The author strongly opposes the opinion of the specialist group of the Japanese Ministry of Health, Labor and Welfare, provided the opinion that no organic lesions have been observed in patients with serious side-effects following cervical cancer vaccine.
Case series (abstract)/ Kinoshita et al, 2014b	Appears to be mainly the same patients being reported in Kinoshita et al, 2014 above.	-
Case report / Tomljenovic et al, 2012 ²⁵	2 adolescents in the US (qHPV)	Post-mortem brain tissue specimens from two young women who suffered from cerebral vasculitis type symptoms following vaccination with qHPV.
Case series / Brinith et al, 2015a ²⁶	53 patients in Denmark included (out of 75 referred for suspected side effects to qHPV vaccination), 38 diagnosed with POTS.	A close chronological association to the vaccination observed. POTS should probably be looked upon as a symptom secondary to another yet unidentified condition rather than as a disease entity of its own. Patients experienced the same degree and pattern of symptoms regardless of the POTS diagnosis.
Case series / Brinith et al, 2015b ²⁷	35 women in Denmark (exposed to qHPV).	Findings from this study neither rule out nor confirm a causal link between symptoms and the HPV vaccine, but do suggest that further research is urgently warranted.
Case series Brinith et al, 2015c ²⁸	39 women in	POTS diagnosed in 55-56% of

²⁵ Tomljenovic et al, (2012) Death after Quadrivalent Human Papillomavirus (HPV) Vaccination: Causal or Coincidental? Pharmaceut. Reg Affairs. 2012, S12:001

²⁶ Brinith et al, 2015 (a) Suspected side effects to the quadrivalent human papilloma vaccine. Dan Med J.;62(4):A5064

²⁷ Brinith et al, 2015 (b) Orthostatic intolerance and postural tachycardia syndrome as suspected adverse effects of vaccination against human papillomavirus: Vaccine; 10.1016

²⁸ Brinith et al, (2015) (c) Is chronic fatigue syndrome/myalgic encephalomyelitis a relevant diagnosis in patients with suspected side effects to human papilloma virus vaccine? International J. of Vaccines and Vaccination 06; 1(1):3.

Study type / reference	Population / setting / exposure	Key result / authors conclusion
	Denmark (exposed to qHPV) who had responded to a questionnaire about symptoms and onset after vaccination.	individuals, while CFS/ME was diagnosed in 87-90% The authors cannot confirm or dismiss a causal link between HPV vaccine and the disabling symptoms. A consensus on classification is needed.
Case report / Tomljenovic et al, 2014 ²⁹	1 girl in US (qHPV)	The authors felt that this case clearly fulfils the criteria for POTS/CFS. In addition, the patient fulfilled the first 2 major criteria and 3 minor criteria for Autoimmune/autoinflammatory Syndrome Induced by Adjuvant (ASIA).

Brinth et al, 2015 (a) Suspected side effects to the quadrivalent human papilloma vaccine. Dan Med J; 62(4):A5064

This first paper refers to 75 patients referred to the Frederiksberg Hospital Syncope Unit from May 2011 to December 2014 for a head-up tilt test due to orthostatic intolerance and symptoms compatible with autonomic dysfunction as suspected side effects following vaccination with Gardasil.

The paper states that patients were interviewed with a special focus on symptoms and on the temporal association between vaccination and symptom onset and that the narrative report was supplemented by the short form of the International Physical Activity Questionnaire (IPAQ-SF) quantifying the patient's physical activity at the time of referral and just before vaccinations on a recall basis. Patients were excluded if they could not account for the temporal association between vaccination and symptom onset, had possible triggering factors other than vaccination or had chronic pre-existing illness.

Only 53 patients were included who reported onset of symptoms consistent with autonomic dysfunction within the first two months post-vaccination. In this paper, the mean age at symptom onset was 21.0 ± 7.4 years (range: 12-39 years). The mean time between vaccination and onset of symptoms was 11.1 ± 12.5 days (range: 0-58 days) and symptoms were reported to appear after the first vaccination in 21 patients (40%), after the second vaccination in 19 patients (36%), and after the third vaccination in 13 patients (25%). The overall distribution of time-to-onset and the relation between time to onset and clinical presentation is, however, not fully interpretable since patients where time to onset is longer than 2 months or uncertain have been excluded from the study.

Based on the physical activity questionnaire, 67% had a high and 33% had a moderate activity level before symptom onset. Five patients had a very high activity level and were competing on a national or international level in their sport.

Twenty eight (53%) patients were diagnosed with POTS at tilt table test.

²⁹ Tomljenovic et al, (2014) Postural Orthostatic Tachycardia With Chronic Fatigue After HPV Vaccination as Part of the "Autoimmune/Auto-inflammatory Syndrome Induced by Adjuvants". J Investig Med High Impact Case Rep.; 2(1): 2324709614527812.

The authors conclude that POTS should probably be looked upon as a symptom secondary to another yet unidentified condition rather than as a disease entity of its own. This is underscored by the fact that patients experienced the same degree and pattern of symptoms regardless of the POTS diagnosis.

Brinth et al. 2015(b) Orthostatic intolerance and postural tachycardia syndrome as suspected adverse effects of vaccination against human papillomavirus: Vaccine; 10.1016

This second paper described the frequency of symptoms in a group of patients consecutively referred to the same syncope unit for the same reason as stated above. This paper describes only 35 patients. There is no reference to how this specific subset of cases was selected for inclusion in the analysis.

This publication additionally included an analysis of blood tests, as well as use of a specific questionnaire (COMPASS 31) to evaluate the severity of specified symptoms of autonomic dysfunction. The mean age at onset of symptoms was 22.0 years (range: 12–39). There was a mean delay between vaccination and onset of symptoms of 9.3 days (range: 0–30), and mean time between onset of symptoms and examination was 1.9 years (range: 0–5). Symptoms were reported to appear after the first vaccination in 24%, after the second vaccination in 51%, and after the third vaccination in 25%. Twenty-one of the referred patients (60%) fulfilled the criteria for a diagnosis of POTS.

Before symptom onset 71% of the patients had a high and 29% had a moderate activity level. As stated in the first publication, half of those with a high activity level were competing at a national or international level in their sport. Twenty-four of the 35 patients used oral contraception. The remaining 11 patients all reported irregular periods. Median serum bilirubin level was 5 (ranging from below detection limit to 13 micromol) All other laboratory tests were within normal range.

The authors comment that the observed low levels of bilirubin may have affected the immune response to vaccination, and that high levels of physical activity may increase both pro- and anti-inflammatory cytokines as well as leukocyte subsets. They also suggest that irregular periods could contribute to development of autoimmune conditions. Coupled with references to a study that suggested exercise may enhance the immune response to vaccination and other data suggesting gender-based differences in immune responses to endurance exercise, the authors' hypothesis is that all of these factors could increase the susceptibility to HPV vaccine-induced reactions in this subset of vaccinees.

Brinth et al, 2015 (c), Is chronic fatigue syndrome/myalgic encephalomyelitis a relevant diagnosis in patients with suspected side effects to human papilloma virus vaccine? International Journal of Vaccines and Vaccination 06; 1(1):3.

This third publication reports on the same case series as the previous two publications. A total of 90 patients are presented, referred to the syncope unit from May 2011 to April 2015, assuming an additional 15 referrals between December 2014 and April 2015. However, in this paper the authors investigated to what extent these patients fulfilled the diagnostic criteria for chronic fatigue syndrome (CFS).

The authors included 39 of the 90 subjects who voluntarily responded to a questionnaire about symptoms and onset following vaccination.

The study included 39 girls/women aged 22.9 ± 7.2 years (mean \pm sd) (range 13–39) at time of examination. Twenty of the patients (51%) fulfilled the criteria for a diagnosis of POTS. Thirty-four (87%) and 35 (90%) of the patients fulfilled the Canadian and Institute of Medicine (IOM) criteria for CFS/ME (myalgic encephalomyelitis), respectively. POTS was diagnosed in 56% and 55% of patients who fulfilled the Canadian and the IOM CFS/ME criteria, respectively.

Evaluation of the Brinth and colleagues (2015, a,b,c) case series

In these three papers from Brinth and colleagues (2015a, b, c), all patients were referred to the same syncope unit for evaluation for an existing concern of HPV vaccine-induced illness. This reason for referral in itself makes the case series unrepresentative of the general population who may present for evaluation and diagnosis of such illnesses.

It is clear from the first paper that patients were excluded if they do not meet a pre-defined hypothesis of vaccine-induced illness (symptoms prior to vaccination, onset greater than 2 months after vaccination, unknown onset time or if other causes could be found). Patients were included in the third paper based only on voluntary responses to a questionnaire. The consistency in symptom profile across the case series is highlighted in the papers. However, it is unclear whether or not the absence or presence of specific symptoms was solicited by the interviewer, although the presentation of results suggests this was the case. If so, then it is perhaps not surprising that such a selected case series interviewed retrospectively in this way would yield these symptom characteristics. Furthermore, many of these symptoms would require some sort of objective clinical evaluation, yet there is no information on how this was done or what other clinical assessment may have been undertaken to exclude other causes of the symptoms.

As the initial symptoms of POTS and autonomic dysfunction most likely have an insidious onset, objective recall of exact symptom onset (as well as the date/trigger for the symptoms) will be difficult to achieve. This is particularly so given that the mean time between onset of symptoms and examination was stated as 1.9 years (range: 0–5). The reliability and objectivity of such recall is questionable, and inherent recall bias in the methods is likely.

Although the case series included only patients with self-reported symptom onset within 2 months of vaccination, it is notable that the mean reported onset time after vaccination was very short at around 9 to 11 days (with day zero included in the range). The authors suggested that these symptoms could be caused by an autoimmune response to the vaccine. However, a short onset would not necessarily support this, on the basis that it would take longer for the body to mount a specific auto-immune response and then for this to have an obvious clinical consequence. The lack of any consistent relationship with the dose sequence also does not support the notion that this case series is suggestive of a specific autoimmune response to the vaccine.

Furthermore, there appears to be no correlation between the likely age-specific exposure to HPV vaccine in the Danish population and the age characteristics of these patients at symptom onset. The mean age of vaccinees in Denmark from May 2011 to April 2015 was most likely closer to 12 years, yet the mean age of the case series was 21 years (17% were aged between 12 and 15 years, 21% between 15 and 19 years, 37% between 19 and 27 years, and 25% were 27 years or older). If HPV vaccine was a cause of the reported symptoms, a lower mean age of symptom onset amongst the case series and a distribution of ages more closely aligned to the likely age-specific vaccine exposure could be expected.

Finally, in this case series two thirds of patients had a high level of physical activity (one third had a moderate level) prior to symptom onset, half of whom were competing at a national or international level in their sport. Based on this, the authors suggested that exercise may be a risk factor for HPV vaccine-induced illness. However, available medical literature on POTS suggests that high athletic (and academic) achievement is a common pre-existing characteristic of POTS sufferers in general. The authors' suggestion that high levels of physical activity in females, whether or not coupled with low

bilirubin levels and irregular periods, is a risk factor for vaccine-induced injury is not supported by the data.

Taken together, it is considered that the case series is compatible with the natural background characteristics and epidemiology of POTS (and chronic fatigue-like syndromes) in those eligible for vaccination in Denmark (and other countries). This is further supported by the authors' analysis in the third paper.

There is evidence in the medical literature that up to 40% of patients diagnosed with POTS also meet the diagnostic criteria for CFS, with some authors suggesting the overlap could be higher. The finding by Brinth and colleagues (2015 c) that just over half of their case series fulfilling a CFS diagnosis also meet the criteria for POTS is therefore consistent with the background epidemiology of POTS in the absence of HPV vaccine exposure. The authors now suggest that CFS should be considered as a diagnosis in patients who report chronic symptoms of orthostatic intolerance and autonomic dysfunction following HPV vaccine (whether or not they also meet the POTS criteria). In this paper, the authors acknowledge the published study (Donegan et al, 2013)¹² which found no evidence of an increased risk of CFS following bivalent HPV vaccine (Cervarix) but consider this to be of limited value, based on the assumption that CFS is under-diagnosed in the UK. The results of the study by Donegan and colleagues (2013) which used a self-controlled case series method, are presented in section 2.2.4.2 below. Such methodology only uses vaccinated cases, however, even if one assumes that CFS is under-diagnosed in the UK, there is no good reason to suspect that this would apply differentially to vaccinated and non-vaccinated subjects. Furthermore, the UK study included a sensitivity analysis of cases referred by their General Practitioner for symptoms of chronic fatigue, but had not yet received a diagnosis.

Overall, the case series reported by Brinth and colleagues (2015) is considered to represent a highly selected sample of patients, apparently chosen to fit a pre-specified hypothesis of vaccine-induced injury. The methods used to ascertain the trigger and time to onset of specified symptoms of autonomic dysfunction may inherently bias patient recall. Whilst Brinth and colleagues (2015) acknowledge that their case series cannot prove a causal association with HPV vaccine, they do not acknowledge or discuss the possibility that their case series simply reflects the expected characteristics and prevalence of POTS and autonomic dysfunction amongst a population cohort with 90% vaccine uptake. The authors speculate that high intensity physical exercise may be a risk factor for development of HPV vaccine-induced illness, but do not reflect upon the available medical literature suggesting that this is a commonly-reported characteristic in POTS patients, regardless of putative trigger. Finally, Brinth and colleagues (2015) now propose that their case series should be considered as having CFS induced by HPV vaccine and that this requires further, robust study, but dismiss an existing study that has already tested this hypothesis and found no association.

2.2.4. Other data

The PRAC reviewed reports submitted by Member States, additional data from the Eudravigilance, and data submitted voluntarily by the public.

2.2.4.1. Overview of Danish report

The Danish Health and Medicines Authority (DHMA) submitted a report for consideration by PRAC as part of the ongoing assessment, titled "Report from the Danish Health and Medicines Authority for

consideration by EMA and rapporteurs in relation to the assessment of the safety profile of HPV-vaccines³⁰.

The Danish report includes a descriptive overview of serious suspected adverse drug reactions (ADR) reports following HPV vaccine from Denmark, a summary of available literature, comparative analysis of worldwide data provided to the Danish Health and Medicines Authority by the Uppsala monitoring centre and a summary of the situation in Japan.

The case series analyses from Brinth and colleagues (2015) at a syncope centre based in Copenhagen, were referred to in the Danish Health and Medicines Authority report. These publications are presented and considered in detail in section 2.2.3 above.

The overview of all reports received by the Danish Health and Medicines Authority shows that the number of reports have increased over time but also correlated to the number of doses distributed for the vaccine.

Table 9 - Total number of ADR reports received by the Danish Health and Medicines Authority between 2009-Q1 2015, and corresponding number of doses of HPV vaccine distributed

HPV vaccine	2009	2010	2011	2012	2013	2014	Q1 2015	Total
Number of reports	288	66	43	96	511	224	77*	1305
– of which serious	25	5	6	18	177	91	41	363
Number of doses sold	347,690	151,476	163,374	349,730	488,224	114,457	20,817	1,635,768

*The number of reports received in 2015 including both Q1-Q2 is 385

The Danish report includes a descriptive overview of all spontaneous serious suspected ADRs (n=363) received up to 19 March 2015. Based on a review of the most recently received reports, 5 main symptom categories were identified by the Danish Health and Medicines Authority based on the reviewers impression of the symptoms relatedness within each category, as well as frequency and severity of occurrence; severe fatigue, neurologic symptoms, circulatory symptoms, pain and headache. Eight additional categories were added, that included frequently reported terms; autonomic imbalance, abdominal discomfort, urinary tract symptoms, allergy, infections, menstrual disorder, thermal dysregulation and malaise.

The Danish report did not evaluate any causal or temporal relation between the symptoms reported and the HPV vaccine exposure, as information about time of symptom onset and duration was too often missing or not accurate.

The most frequently reported symptoms in the serious reports were (ranked order of symptoms occurring in more than 100 cases): headache, pain, dizziness, malaise, fatigue, paresthesia and

³⁰ <http://sundhedsstyrelsen.dk/~media/0A404AD71555435BB311CD59CB63071A.ashx>

cognitive disorder. The Danish report states that the review identified 40 reports with verified diagnoses of POTS.

Around 45% of the serious reports were received from non-health care professionals (consumers or lawyers) and among the serious consumer reports about half of them have been medically confirmed.

Of the 363 reports, 77 (21%) had a well-defined, specific diagnosis of an adverse reaction. Of the remaining reports, 44 % had symptoms in 4 or 5 of the 5 main categories. A total of 62 of 117 cases (53 %) reporting fatigue were reportedly associated with a social handicap, i.e. reduced ability to attend school or work or carry out daily activities. For 17 % of all patients considerable impact on daily life was described. The most frequently occurring of the 8 additional categories were malaise, abdominal discomfort, autonomic imbalance, infections and thermal dysregulation in that order.

The overall reporting rate of all suspected ADRs in Denmark is ~0.8 per 1,000 doses distributed. Aside from the specific case reports under evaluation in this review and discussed separately, this overall reporting rate is similar to the overall suspected ADR reporting rate in the UK (~ 1 per 1,000 doses administered), or the global suspected ADR reporting rate (~180,000 adverse events per 165 million doses distributed; or ~ 1.1 per 1,000 doses). The reporting rate of serious suspected ADRs in Denmark is ~0.22/1,000 doses, also similar to the reporting rate in the UK (~0.24/1,000 doses).

There was a notable increase in serious suspected ADRs in 2013 and, as acknowledged in the Danish report, the characteristics of these reports in Denmark was likely to be influenced by the publicity in Denmark.

As most of the reports do not have a specific diagnosis but an overlapping range of symptoms, the report states that the ADR reports show similarity to CFS. Based on an analysis of data provided by the Uppsala monitoring centre (see below), the Danish report argues that there is an increasing trend in worldwide reports that could fit this category of undiagnosed but similar 'chronic fatigue-like syndrome' which may be specific to HPV vaccine.

The PRAC noted the descriptive analysis submitted by the Danish Health and Medicines Authority but concluded that it is not sufficient to inform the causality assessment in the context of the referral.

The majority of reports of POTS from Denmark have been reported by a Copenhagen-based syncope centre, and are therefore most likely the same case series described by Brinth and colleagues in their three publications to date (Brinth et al, 2015 a, b and c). These three publications are summarised and discussed in section 2.2.3 above.

Information provided to the Danish Health and Medicines Authority by the Uppsala Monitoring Centre

At the request of the Danish Health and Medicines Authority, the Uppsala Monitoring Centre has provided an overview of worldwide suspected ADRs associated with HPV vaccines from Vigibase. Vigibase is an international drug safety database sponsored by the World Health Organisation. This overview focused on POTS, CRPS, CFS, myalgic encephalitis (ME)/post viral fatigue syndrome (PVFS), fibromyalgia, and reports without a specific diagnosis but including symptoms that may potentially relate to autonomic dysfunction.

As of 3 August 2015, Vigibase contained 147 reports with the MedDRA³¹ term POTS associated with HPV vaccines. Vigibase also included the following reports in association with HPV vaccines - 94 CRPS,

³¹ The Medical Dictionary for Regulatory Activities (MedDRA) is a rich and highly specific standardised medical terminology developed by the International Conference on Harmonisation (ICH) to facilitate sharing of regulatory information internationally for medical products used by humans. It is used for registration, documentation and safety monitoring of medical products both before and after a product has been authorised for sale. Products covered by the scope of MedDRA include pharmaceuticals, vaccines and drug-device combination products. <http://www.ich.org/products/meddra.html>

94 CFS, 62 ME/PVFS and 87 fibromyalgia. Most reports for each of these preferred terms (PTs)³² originated in the US. Denmark and Japan reported the second highest number of POTS and CRPS, respectively. The UK reported the second highest number of CFS, ME/PVFS.

Fibromyalgia, CFS and ME/PVFS have been reported relatively constantly since 2009 (with a slight decrease in 2011/12), but reports of POTS and CRPS had notably increased since 2013. It is not stated in the Uppsala monitoring centre report if these dates relate to symptom onset, diagnosis or report receipt date, although the latter is most likely.

The Uppsala Monitoring Centre report highlights that there is consistency between the WHO database and the Danish database in the top 20 reported events for HPV vaccines, with 60% similarity in the listing of the top 10 events. It then states that the comparison of HPV vaccines to all other vaccines in females, showed a difference to all other vaccines (febrile and general signs and symptoms: fever, nausea, and headache).

The first analysis compared 549 HPV vaccine reports from Denmark vs 45,327 worldwide HPV vaccine reports received for females between the age of 9 to 25 years. This analysis appears to have included all events, rather than only serious events. However, given that Denmark had received 1,228 reports (322 serious) up to Q1 2015, it is unclear how the 549 reports were selected.

This analysis showed the terms POTS, orthostatic intolerance and autonomic nervous system imbalance are reported disproportionately more in HPV reports from Denmark vs HPV reports in other countries. Eczema, sensory disturbance, disturbance in attention, memory impairment, palpitations, cognitive disorder, fatigue, infection, visual impairment, influenza-like illness, muscle spasms, and arthralgia also show disproportionality.

The second analysis compared 45,876 worldwide HPV vaccine reports against 79,678 worldwide reports for all other vaccines combined and received for females between the age of 9 to 25 years.

It was found that disproportionately more HPV vaccine reports were coded as serious compared to other vaccine reports. Malaysia, Italy, Japan, Denmark, and Australia report disproportionately more HPV vaccine reports compared to other vaccines, whilst Canada, the UK, Sweden, and France report disproportionately fewer HPV vaccine reports compared to other vaccines.

In terms of reporting within MedDRA System Organ Class (SOC), disproportionately more HPV vaccine reports related to Reproductive system, the Investigations SOC, Surgical and medical procedures, Nervous system disorders and Psychiatric disorders SOC, Social circumstances, Neoplasms and Injury and poisoning are received compared to other vaccines.

POTS had been reported 82 times for HPV vaccine and 1 time for other vaccines (0.2% vs 0.0%), CRPS: 69 times for HPV vaccine and 16 times for other vaccines (0.2% vs 0.0%), autonomic nervous system imbalance: 76 times for HPV vaccine and 16 times for other vaccines (0.2% vs 0.0%), CFS: 65 for HPV vaccine and 30 times for other vaccines (0.1% vs 0.0%), fibromyalgia: 62 times for HPV vaccine and 39 times for other vaccines (0.1% vs 0.1%) and PVFS: 47 times and 53 times for other vaccines (0.1% and 0.1%).

In its conclusions, the Uppsala monitoring centre report highlights an overlap in symptoms in reported cases of POTS, CRPS, CFS, PVFS and fibromyalgia, notably fatigue, headache and dizziness. Whilst it acknowledges that these symptoms are non-specific and are commonly occurring events, it notes that the reports of POTS, CFS and PVFS from which these events arose have been largely classified as

³² A preferred term (PT) is a distinct descriptor (single medical concept) for a symptom, sign, disease, diagnosis, therapeutic indication, investigation, surgical, or medical procedure, and medical, social, or family history characteristic. http://www.meddra.org/sites/default/files/guidance/file/intguide_18_1_english.pdf

serious reports (POTS 80%, CFS 78%, PVFS 89%) stating the need for hospitalisation and/or resulting in disability or interruption of normal function.

It is further stated that the different levels of reporting of the different syndromes across countries could be explained by the same syndrome being diagnosed/coded differently depending on different national practices.

Evaluation of the Uppsala Monitoring Centre report

It is likely that the apparent increase in reports since 2013 across countries has been stimulated by the concerns in Japan, particularly for CRPS, and Denmark, particularly for POTS. This overall trend in reporting over time is therefore not unexpected given the known influences of media attention on spontaneous reporting. However, as the Uppsala Monitoring Centre report includes no information on the number of doses of vaccine used over this time period, conclusions cannot be drawn on this.

The Uppsala Monitoring Centre report suggests that the same clinical 'syndrome' may be occurring following HPV vaccination but is being diagnosed/coded differently across countries. Whilst it cannot be excluded that this is the case, many factors influence the levels of reporting (e.g. the US accounts for about half of the worldwide use of Gardasil, which is a likely reason most reports of each syndrome originate in the US) and the nature of reports submitted (e.g. public awareness of a specific event such as POTS and CRPS will influence this). Overall, the observations included the Uppsala Monitoring Centre report does not allow any conclusions to be made on clinical or diagnostic practice between countries.

In relation to the comparison of the top 20 reported symptoms worldwide from serious reports for HPV vaccines against all other vaccines, the Uppsala Monitoring Centre report concludes that this showed a difference between the HPV vaccine and all other vaccines. However, the comparison actually shows very few differences and a lot of consistency, in terms of the type of event reported at the various age bands. This consistency is perhaps not surprising given that the majority of these top 20 serious events include the signs and symptoms (or related terms) of the most common, expected events of most vaccines given to adults and adolescents, which are usually transient. Many of these top 20 reports may also include the signs and symptoms of immediate faints following vaccination. Many of these are also already included in the product information for HPV vaccines.

CFS and PVFS/ME showed no statistically significant disproportionate reporting for HPV vaccine, nor did it show a very wide range of more relevant and more specific higher level terms that may potentially include symptoms of undiagnosed CFS (as well as POTS, CRPS, PVFS and fibromyalgia). This includes, autonomic nervous system disorders, asthenic conditions, GI motility disorders, tachyarrhythmia, cognitive disorders, postural dizziness, muscular weakness, mobility decreased, exercise tolerance decreased, various pain terms, and skin discolouration. Although the numbers are small for the non-HPV vaccine group, this comparison argues against such reporting patterns pointing to a specific undiagnosed 'syndrome' reported with HPV.

Of these more relevant and specific higher level terms, only asthenic conditions shows any apparent disproportionality and this only occurred when the decision was taken to lower the 'signal threshold', but this was only marginal (12.3% of HPV vaccine reports vs 9.3% of other vaccine reports). It should be noted that this higher level term includes fatigue, which is one of the most common adverse effects of any adult or adolescent vaccine. Possibly the most relevant terms that showed some disproportionality were syncope, presyncope, muscular weakness and activities of daily living impaired. However, this is a very small number of PTs, and there are many more relevant and more specific PTs that did not show any disproportionality for HPV vaccines. Overall, the data show no specific reporting

profile for HPV vaccine compared to other vaccines that may indicate a particular undiagnosed syndrome.

The analysis of Danish HPV events vs worldwide HPV events showed that the terms POTS, orthostatic intolerance and autonomic nervous system imbalance are reported disproportionately more vs HPV reports in other countries. However, the report states that other PTs that are also clinically-relevant (to undiagnosed POTS and related syndromes) did not show disproportionality. It is acknowledged in the Uppsala Monitoring Centre report that, aside from Nervous system disorders, arguably the most relevant MedDRA SOCs to consider in order to detect any relevant symptom clusters did not show any apparent disproportionality in reporting for HPV vaccines (General disorders, Gastrointestinal disorders, Musculoskeletal disorders and Cardiac disorders).

The PRAC noted that although the analysis appears to incorporate statistical adjustment, this sort of multiple analysis and data-mining of suspected ADR data (at MedDRA SOC, high level and preferred terms level) will inevitably yield some results of disproportionality for HPV vaccines reports as well as non-HPV reports, as shown in the Uppsala monitoring centre report. However, the approach taken to selection of SOCs, high level and preferred terms, amendment of a pre-specified 'signal threshold' and selective discussion of disproportionate reporting for HPV vaccines does raise questions about the conclusions.

Overall, it is considered that the Uppsala monitoring centre report serves to highlight what is already known, i.e. that some countries are observing an increasing number of reports of different types of adverse events associated with HPV vaccine and that such reporting has increased over time.

Overview of data from Japan

The Danish Health and Medicines Authority report included a brief description of the situation in Japan. It is stated that although the initial concerns in Japan focused on pain and the diagnosis of CRPS, the adverse event reports in the Japanese database have been characterised by a wider variation of symptoms, often difficult to standardise. It states that often reported symptoms were pain, movement disorders, orthostatic intolerance, dizziness, menstrual abnormalities and fatigue. Symptoms were reported to fluctuate and in some patients lasting for a long time. The Danish Health and Medicines Authority report states that the pattern reflects much of the same symptoms as are also reported in the Danish cases.

Overall conclusions on the Danish Health and Medicines Authority report

The Danish Health and Medicines Authority report considers that due to differential clinical practice across countries, similar suspected ADRs to HPV vaccine are receiving different diagnoses (or indeed no clear diagnosis). This theory appears to have prompted the comparative overview of all serious suspected ADRs, including the worldwide data obtained from Uppsala monitoring centre, in order to identify any potential 'non-specific' safety signals.

As many of the serious suspected ADRs reported following HPV vaccine have no confirmed diagnosis but a wide range of overlapping symptoms, and based on hypotheses that POTS, CRPS, fibromyalgia and CFS may have a common pathophysiology (i.e. autonomic dysfunction, possibly due to small fibre neuropathy), the Danish Health and Medicines Authority report proposes that the constellation of symptoms and reports should be considered as 'chronic fatigue-like' illness, which accords with the current opinion of Brinth and colleagues (2015c). It is difficult to formally diagnose CFS from the available reports but the collection of features in many of them may be seen as suggestive of CFS.

Several studies relevant to POTS and CRPS are referred to in the Danish Health and Medicines Authority report. The report also refers to studies looking at a range of autoimmune disorders, other serious events and CFS. These were generally large studies that used electronic health record data and used a variety of study designs, from cohort, case control and risk interval or self-controlled case series analysis. None of the studies found conclusive evidence of increased risks for the included outcomes.

The Danish Health and Medicines Authority report then comments on the limitations of studies which use 'registers' (which is presumed to mean electronic health record data) as they consider data capture in this case is highly dependent on diagnosis. The report argues that because the adverse events being reported following HPV vaccine are difficult to diagnose and have overlapping symptoms, the currently-available studies could not identify cases relevant to the current issue.

Of course, any such observational study will have limitations, as well as strengths. It is important that, when relevant to the objectives, observational studies are based on medically-diagnosed illness using valid case definitions, and the study should minimise information bias (such as differential diagnostic likelihood/practice between the groups under comparison). It is acknowledged that not all of these studies included outcomes that are directly relevant to the current review. However, the Danish Health and Medicines Authority report under-estimates the value of two of these studies to the current issue, which are considered further in section 2.2.4.2 below.

2.2.4.2. Additional studies

The following two studies from literature publications were also considered relevant to the review:

Klein et al, (2012) Safety of Quadrivalent Human Papillomavirus Vaccine Administered Routinely to Females. Arch Pediatr Adolesc Med. 2012;166(12):1140-1148.

The study by Klein and colleagues (2012)³³ was not reliant on diagnosed illness, and evaluated hospital visits amongst 189,629 females aged 9 to 26 years for a very wide variety of clinical reasons (256 ICD categories were included, based on discharge coding) within 14 and 60 days of vaccination (the study used risk interval analysis). An increased risk for syncope was identified only on the day of vaccination. Other categories included that could be relevant to the current issue were "Hereditary and degenerative nervous system conditions" (which included the subcategory of autonomic nervous system disorders), ear disorders (which included the subcategory of dizziness), "ill-defined conditions and factors influencing health status" (which also included the subcategory of malaise and fatigue). There were very few cases in the category that would have included a discharge summary for autonomic nervous system disorders, and discharges for malaise and fatigue were not significantly raised in the post vaccine risk period following adjustment for multiple analyses. Ear conditions showed a slightly elevated risk, but individual case review revealed most events were either present before vaccination, were opportunistic evaluation/coding at the vaccine visit, or had obvious aetiologies not associated with vaccination (it is not stated if or how many cases of dizziness contributed to this category).

Although this study did not evaluate CRPS and POTS and was largely a data-mining exercise, it does give some insight into the general behaviour in a large cohort following vaccination for a wide variety of clinical reasons, and revealed no obvious clusters of concern.

³³ Klein et al, (2012) Safety of Quadrivalent Human Papillomavirus Vaccine Administered Routinely to Females. Arch Pediatr Adolesc Med.;166(12):1140-1148.

Donegan et al (2013) Bivalent human papillomavirus vaccine and the risk of fatigue syndromes in girls in the UK. Vaccine; 31(43): 4961-7

In this study, O/E analyses were conducted comparing the number of reports of fatigue syndromes submitted with what would be expected in the target population. Subsequently, an ecological analysis and a self-controlled case series compared the incidence rate of fatigue syndromes in girls before and after the start of the vaccination campaign and the risk in the year post-vaccination compared to other periods.

The O/E analysis showed that the number of spontaneous reports of chronic fatigue following Cervarix vaccination was consistent with estimated background rates even assuming low reporting. Ecological analyses suggested that there had been no change in the incidence of fatigue syndromes in girls aged 12-20 years after the introduction of the vaccination despite high uptake (IRR: 0.94, 95% CI: 0.78-1.14). The self-controlled case series, including 187 girls, also showed no evidence of an increased risk of fatigue syndromes in the year post first vaccination (IRR: 1.07, 95% CI: 0.57-2.00, $p=0.84$).

The study by Donegan and colleagues (2013), as well as using the self-controlled case series design (and therefore avoiding the issue of differential diagnostic practice in vaccinated and unvaccinated), evaluated not only diagnosed CFS, but also referrals from General Practice for as yet undiagnosed symptoms of chronic fatigue and exhaustion, as well as diagnoses for fibromyalgia, post viral syndrome and neurasthenia. The study found no association between HPV vaccine and any of the conditions studied and was powered to detect a relative risk of 3 or more.

The study by Donegan and colleagues does not address all of the current issues. The study period only allowed Cervarix-exposed subjects to be included. Although the study included conditions related to CFS such as fibromyalgia, CRPS and POTS were not specifically studied. However, given the current suggestion in the DHMA report that the constellation of undiagnosed symptoms should be considered a chronic fatigue-like syndrome, as CFS and POTS are known to have a high level of overlap, and as Brinth and colleagues (2015c) now consider that CFS may be a more relevant diagnosis in the Danish cases, the study by Donegan and colleagues (2013) is a relevant epidemiological study for the this review.

2.2.4.3. Data from Eudravigilance

Up to 07 August 2015, 22 cases of CRPS have been reported in the European Medicines Agency's safety database, Eudravigilance, in girls between 12 and 17 years old with Cervarix and 35 cases with Gardasil/Silgard in the same age range who belong to the target population for HPV vaccination. Most of the cases have occurred in Japan. These two observations may be explained by the initial concerns regarding HPV vaccines and CRPS having originated in Japan.

Eleven (11) cases of POTS have been reported in the Eudravigilance database in girls between 12 and 17 years old with Cervarix and 60 cases in the same age group with Gardasil/Silgard. Most of these cases have occurred in Denmark, USA and UK.

No reports on Gardasil 9 were identified in Eudravigilance database.

2.2.4.4. Data from Netherlands Pharmacovigilance centre LAREB

The PRAC also received a report from the Dutch Pharmacovigilance centre LAREB, which was intended to share the experience from the Netherlands with the PRAC. This report contained information on the suspected ADR reports received since the introduction of the HPV vaccination in the Dutch population.

From the start of the national immunisation program in the Netherlands in January 2009 up to 25 August 2015, in total 1239 reports have been received. The report from LAREB focussed on the increased retrospective reporting of suspected ADRs following media interest during the summer of 2015. Neither CRPS nor POTS were reported in the Netherlands as suspected ADRs in association with HPV vaccines.

The LAREB report concludes that the results presented in their report are based on spontaneous reporting, which is a signal generating methodology, sensitive to media attention. It is also commented that these data cannot be used to determine if there is any causal relationship between the reported event and the HPV vaccine. The PRAC agreed with the conclusion by LAREB.

2.2.4.5. Data submitted by the public

A large amount of information was received from the public in Denmark, France, Ireland, Italy, Spain, Sweden and the United Kingdom. This current assessment is focused on CRPS and POTS, and the submissions included a very wide range of other information and variable symptoms. The relevant submitted data are summarised here and were given full consideration by PRAC.

This information consisted of descriptions of individual experiences, of surveys the patients/parents had undertaken and summarised. In addition, these submissions commented on problems encountered with trying to report and record suspected side effects accurately, official statistics on number of adverse reactions recorded by National competent authorities and concerns about accuracy and quality of the data provided. Finally, these submissions also provided a list of actions which the patient/parent groups proposed to be undertaken.

The PRAC noted that within the submitted information, there were a number of detailed descriptions of young girls suffering from debilitating and long-lasting conditions. There was a wide range of symptoms, many of which were similar to those considered elsewhere in this referral assessment in the context of POTS and CRPS, but also including seizures, other neurological and psychiatric symptoms and pain, but with no apparent diagnosis. The clinical characteristics were highly variable.

As symptoms are highly varied and unspecific without a clear definition of the underlying pathophysiological mechanism finding adequate healthcare was a common problem in these reports. These conditions also occur in individuals who have not been exposed to HPV vaccines and were described long before introduction of the HPV vaccines. In general, the cases described appear to have similar characteristics to cases ascertained from other sources in this review. No pattern in terms of time-to-onset or association with a particular dose was seen. Co-morbidities and complex symptom combinations further complicate causality assessment. The CFS described in many of these cases has some symptom overlap with POTS. This is further discussed elsewhere in this report (see Section 2.2.3).

It is acknowledged that the patients/ parents refer to a range of other disorders which they describe as possible side effects to HPV vaccine. When taking the totality of data in the referral into account, it is the opinion of the PRAC that these reports do not suggest a causal link to the HPV vaccines.

3. Expert consultation

The PRAC consulted the Scientific advisory group (SAG) on vaccines on 21 October 2015 which provided advice on a number of issues. The expertise of the SAG was enriched by experts on the syndromes, on neurology, cardiology and pharmacoepidemiology. The questions that PRAC asked the SAG and their answers are presented below.

1. What is the current understanding about the pathophysiology of Complex Regional Pain Syndrome (CRPS) and Postural Orthostatic Tachycardia Syndrome (POTS)?

CRPS is defined as continuing pain that is disproportionate to the inciting event, may be associated with dysautonomic signs and symptoms and is usually confined to a single limb. Other symptoms, including psychological symptoms are recognised, particularly amongst those with more persistent pain. CRPS typically follows an episode of trauma including fracture of the wrist or carpal tunnel syndrome surgery, or immobilisation of the limb. The experts were not familiar with cases in which needle trauma from an immunisation had triggered an episode of CRPS. Consequently, the onset of symptoms of CRPS are difficult to define because the syndrome is usually only diagnosed from the point when normal recovery from the initiating trauma should have occurred (may be as much as 5-7 weeks post-trauma), and is usually only recognised some time later among those with continuing pain afterwards. The majority of CRPS cases (>70%) improve over time and show no recurrence; recovery is higher in children. The pathogenesis of CRPS is incompletely understood but researchers are investigating genetic, inflammatory, auto-immune and psychological contributors to the condition.

Based on the overall considerations made by the CRPS and pain experts who studied the reports of the cases, the SAG concluded that most of the reported cases ascribed to HPV vaccines, including those from Japan, do not clearly fall into the definition of CRPS as it is currently understood using the available diagnostic criteria. In some of the cases the available information is insufficient to make a diagnosis. In some cases discussed in the referral the long interval from vaccination to onset of symptoms (after one or two years) reduces the plausibility of an association.

POTS is a systemic syndrome which has been known for a long time under different names and is still poorly understood. POTS patients typically show persistent tachycardia for more than 10 minutes upon standing, as well as an increase in heart rate to above 120 bpm or by ≥ 30 bpm, and in children and juveniles below 19 years of age by ≥ 40 bpm, without arterial hypotension. A diagnosis of POTS cannot solely rely on these symptoms; other symptoms (e.g. syncope, fatigue, headaches, light-headedness, diaphoresis, tremor, palpitations, exercise intolerance, near syncope upon standing upright) vary across patients and are otherwise non-specific. Consequently, POTS seems to be defined only if given this label (i.e. a subjective syndrome), but it is otherwise not particularly well characterised. POTS overlaps with orthostatic tachycardia which occurs as a normal physiological response on standing and may be prolonged following a period of bed rest or inactivity as a result of "deconditioning". It was noted that many of the POTS cases that are part of the referral do not fit well into the typical syndrome definition, or are poorly documented or inadequately diagnosed.

Those with the diagnosis of POTS are typically pubertal high achieving girls who are very active and often athletic, may have had recent illness, although stress, surgery, hypermobility in joints, psychological and genetic predisposition may be involved. Fatigue is a common symptom in POTS patients and features of chronic fatigue syndrome (CFS) may dominate. The deconditioning from bed or chair rest (e.g. following an acute illness or CFS), may lead to POTS-like syndrome but can be managed by rehabilitation, and should be differentiated by other cases of POTS which are persistent and particularly debilitating for individuals.

POTS pathophysiology is still poorly understood, and the lack of strict application of diagnostic criteria hampers study of the syndrome. Researchers are currently investigating autonomic dysfunction, autoimmunity and genetic predisposition to POTS, but there is no clear evidence regarding the underlying cause.

The SAG were of the view that the vast majority of the cases after vaccination reported in the literature and database review conducted for the referral do not fit with the accepted definitions of POTS or CRPS and would more appropriately be labelled as having features of CFS. It is currently not clear how many of the remaining reported cases are truly POTS and CRPS, but it seems to be a small proportion of those which have been documented so far. The SAG noted that CFS is difficult to formally diagnose from the available reports but the collection of features fit better than with CRPS or POTS in many of them. It was also noted that some of the patients reported from Denmark had features consistent with CFS and had become deconditioned as a result of fatigue symptoms, such that they also now had features in common with POTS. The cause of CFS is a topic of intense research activity but the pathophysiology of the condition remains unclear in many cases.

The SAG were not aware of any pathophysiological evidence that vaccines in general, or HPV vaccine in particular, leads to CRPS or POTS. Although the association of trauma with CRPS suggests plausibility that the condition might be triggered by a needle, the pain experts did not consider this to be a likely trigger given the lack of cases presenting to the clinics of the assembled experts, despite the large numbers of adolescents receiving immunisations in their countries. The SAG were of the view that the majority of the cases labelled as POTS either didn't fit the accepted definition or seemed to be more likely CFS cases with deconditioning (as a result of fatigue and inactivity). The SAG noted that CFS is rare but reported amongst adolescent girls in developed countries and that the condition is very distressing for the affected individual and their families but usually resolves through adolescence.

2. What is the strength of the available information with respect to the cases of CRPS and POTS which have been reported in girls previously exposed to HPV vaccination?

It was not made explicit by the question whether it should have been interpreted as the strength of the existing information or the strength of the association between the cases of CRPS and POTS and HPV vaccines. The SAG opined to address both elements.

Regarding the strength of the information, the SAG noted the known weakness and limitations of spontaneous passive reporting systems. However, the SAG agreed that spontaneous reporting remains a sensitive tool to pick up unexpected rare signals, which are not predicted at the time of introduction of a vaccine, but its sensitivity for some types of pain, is uncertain. The system was effective in identifying signals which warrant investigation but, because cases might not always be reported, is not as sensitive as active surveillance. A major limitation of the evidence provided is the inadequate reporting of the case definitions in the databases, which may continue to affect future investigations. The SAG noticed that most of the cases presented in the referral could possibly better fit the definition of CFS or at least include some features of chronic fatigue syndrome and less clearly fit the formal definitions of CRPS or POTS.

This observation is important, since a careful study, with better methodology has already been undertaken for CFS. The Clinical Practice Research Datalink (CPRD) study on CFS was found to provide robust data demonstrating a lack of an association between HPV vaccines and CFS.

The O/E analysis conducted by the MAHs in the frame of the referral, and thoroughly assessed by the Rapporteurs, seems to be as robust as it could be, given the difficulties with the type of data gathered and the assumptions made. One of the difficulties mentioned was the background rates estimation; background rates seem to vary across ages and over time possibly due to changes in diagnostic criteria. Some experts considered that expected rates based on the Netherland GP data could be about 30% lower if applying Budapest criteria vs. IASP criteria, which in turn may change some of the signal calculations. However it was noted that the O/E analyses covered a range of scenarios taking into

account uncertainties in both numerator and denominator, and the most plausible scenarios showed no excess of POTS or CRPS cases above the background rate considering the situation in individual countries (e.g. completeness and quality of reporting).

As far as the strength of association between HPV vaccines and POTS and CRPS is concerned, the SAG concluded that an association is not currently supported by the data, although limitations of the data, as mentioned above, must be recognised. Concerning the data that are available from the literature case series, these do not support an association both because of the lack of fit with formal definitions and because of the high risk of bias (e.g. due to lack of the necessary information to assign a diagnosis and interval to onset, or selection of cases with specific time to onset range).

In conclusion, despite the limitations of case series and passive reporting, the SAG agreed that the reports to date do not constitute a signal which would warrant further investigation by the MAH. Ongoing surveillance activities are supported in order to monitor future trends. While the SAG were of the view that the available evidence does not support a causal association, they were aware that additional work to provide further evidence would be helpful from a public health perspective to add to the data available thus far, but would be challenging for the reasons described above.

3. a) Based on the available information, are there specific characteristics that should be monitored in post-marketing surveillance?

There was a clear view from the SAG that enhanced surveillance should continue to be performed. It was noted that there are various mechanisms to obtain information about possible reactions to drugs and vaccines and the public and the health care professionals in Europe are able to report directly.

b) If yes, then:

i. What are these characteristics:

CRPS is coded in international used systems, e.g. MedDRA or ICD10 code, and reference could be made to these. The SAG agreed that 'continuous limb pain' should be used as a non-specific, but possibly sensitive term that could be used to retrieve potential cases of CRPS in safety databases that had not been appropriately labelled as CRPS; although these terms are not specific, using the tight definition of the syndrome might affect the sensitivity of the searches. Flagging search terms prospectively could help in seeking adequate follow-up of potential cases. It is not clear whether these characteristics would change the reporting rates seen, as it should be acknowledged that database searches cannot provide a robust answer because of lack of defined diagnostic codes.

Concerning POTS, it is possible to search for symptoms of the syndrome or specific features of the diagnosis of POTS such as the table-tilt test or heart rate and blood pressure recordings at supine rest and upon standing, which may allow identification of data from safety databases, albeit with limited sensitivity. POTS is coded in MedDRA, however due to the lack of awareness, or even consistent clinical /diagnostic views, around this syndrome in many countries, and due to the difficulties with diagnosis this term might be seldom used. Due to all the uncertainties mentioned, the SAG could not come to a clear conclusion on specific characteristics that could improve case identification in large databases. However, the SAG noted that many POTS cases include features of CFS and that many of the cases labelled as POTS in the review fitted better with a CFS definition such that identification of CFS cases may be valuable in extracting data on POTS.

Considering the possible overlap of CRPS/POTS cases with CFS, which has an established code and a clear set of symptoms, the SAG considered that CFS codes and symptoms could be useful characteristics to be monitored.

- ii. Discuss the feasibility of performing further studies with the potential to provide robust and meaningful results within existing data sources in Europe.

The SAG opinion was that enhanced surveillance should continue as the main pharmacovigilance measure.

In addition, the SAG considered other measures, e.g. population-based registries; the main issue identified with this approach was the risk of bias (i.e. due to enhanced consultation for the outcomes in individuals who know they are vaccinated) and the lack of consistently used diagnostic codes, which may lead to inconclusive results (though it was acknowledged that there is now a Read code for CRPS in CPRD).

Concerning the feasibility of performing studies, overall they might be feasible, despite the challenges due to the large sample size and confounders. However, concern was expressed by the SAG about the risk that studies may lead to results difficult to interpret due to bias, e.g. enhanced ascertainment of vaccinated cases due to media reporting. It was stressed that in any study the method of case ascertainment should be independent of vaccination status as preferential inclusion of vaccinated cases (selection bias) could not be dealt with by statistical methods. Several experts considered only retrospective cohort studies to be potentially of use, and that these should predate media interest.

Finally, the SAG recommended for PRAC consideration that for example the CPRD study, or similar, could be built upon and updated to cover the more recent period previous to the media reporting, and to specifically include the characteristics for CRPS and to increase the sensitivity of some characteristics of CFS to ensure cases which less closely met the case definition could be identified. Such an update may or may not identify more cases than those already identified so far, due to the overlap in syndromes; however there may be some benefit in looking again at the definitions based on the current reporting, as it may shed some further light on CRPS and POTS in association with HPV vaccines.

If retrospective register-based studies are taken, MAHs or public health authorities should carefully consider whether the coding of conditions would adequately capture the diagnosis of POTS, CRPS and CFS, or other relevant search terms and whether there are potential sources of ascertainment bias.

In conclusion, as far as feasibility of further studies is concerned, there are some designs which perhaps the PRAC could consider (e.g. CPRD study or similar retrospective designs), being aware of the risk of bias; however, in light of the lack of a signal so far from case reports, the question remains whether these are warranted at this stage.

4. Pharmacovigilance activities

The PRAC considered that the pharmacovigilance activities that are currently in place for the HPV vaccines should continue. This includes that close monitoring of these syndromes in relation to HPV vaccines should persist. Targeted questionnaires are already in place for CRPS and POTS and these are sent to reporters by the MAHs to obtain more complete information in relation to these reports. In light of the recommendations of the SAG, consideration should be given to how these questionnaires need to be updated.

More specifically, 'continuous limb pain' should be used as a non-specific, but possibly sensitive, term to retrieve potential cases of CRPS that had not been appropriately labelled as CRPS. Specific features of the diagnosis of POTS, such as the tilt table test or heart rate and blood pressure recordings at rest and upon standing, should be monitored. Furthermore, CFS has a clear set of symptoms, which should be monitored due to the possible overlap of POTS cases with CFS.

The PRAC also considered whether any additional pharmacoepidemiological studies should be requested from the MAHs. Taking into account the O/E analyses, which do not suggest an increased occurrence of CRPS or POTS in relation to the HPV vaccines, alongside the advice of the SAG regarding difficulty of reliable capture and identification of these outcomes in healthcare databases and the risk of bias, it was concluded that requesting such studies from the MAHs was not warranted.

Nevertheless, the PRAC acknowledged that further research in the area of both CRPS and POTS, may be beneficial in improving the general understanding of these syndromes, and thereby possibly improve the care of these patients, irrespective of any HPV vaccine exposure.

5. Overall discussion and conclusions

Human papillomavirus (HPV) vaccines have been authorised in the European Union since 2006 for the prevention of cervical and various other cancers caused by HPV infection. Routine surveillance of suspected adverse reaction reports has raised questions on the potential association between the use of the vaccines and two syndromes in particular, which are known as CRPS and POTS. These syndromes have been subject to previous repeated review by PRAC.

On 09 July 2015 the European Commission therefore triggered a procedure under Article 20 of Regulation (EC) No 726/2004 resulting from pharmacovigilance data, and requested the EMA to assess these concerns.

The PRAC requested data and analyses from the MAHs regarding CRPS and POTS from clinical trials and post-marketing safety data, and took into account literature review, data from Eudravigilance, reports submitted by Member States, including Denmark, as well as information from Japan and information submitted voluntarily by the public. The advice of the Scientific advisory group (SAG) on vaccines was sought; the expertise of this group was supplemented with additional European experts on these syndromes and on neurology, cardiology and pharmacoepidemiology.

CRPS

CRPS is defined as continuing pain that is disproportionate to the inciting event and may be associated with dysautonomic signs and symptoms and is usually confined to a single limb. CRPS typically follows an episode of trauma including fracture of the wrist or carpal tunnel syndrome surgery, or immobilisation of the limb. The onset of symptoms of CRPS is difficult to define because the syndrome is usually only diagnosed from the point when normal recovery from the initiating trauma should have occurred, and is usually only recognised sometime later among those with continuing pain afterwards. Available estimates suggest that in the general population around 150 girls and young women per million aged 10 to 19 years may develop CRPS each year.

In the review of clinical trial data a total of 60,594 subjects were included for Gardasil/Silgard and Gardasil 9 and 42,047 subjects for Cervarix. No cases were identified in the Cervarix and comparator cohorts. The incidence of CRPS in the Gardasil/Silgard and Gardasil 9 clinical trials was less than 1 case per 10,000 person-years and comparable in the Gardasil/Silgard and Gardasil 9 and corresponding placebo cohorts.

Analyses of observed versus expected number of spontaneous reports were undertaken, covering a wide range of scenarios regarding underreporting (from 1 – 100 % reporting) and including reports that did not fully meet the diagnostic criteria for the syndrome.

Overall, the comparisons of observed versus expected number of spontaneous reports do not suggest an increased occurrence of CRPS in relation to the HPV vaccines.

Furthermore, the detailed review of the reports of CRPS did not show a consistent pattern regarding time-to-onset following vaccination or clinical characteristics.

The SAG also concluded that most of the reports of CRPS under review did not appear to fulfil the established diagnostic criteria for CRPS.

Overall, available data do not provide support for a causal association between HPV vaccines and CRPS.

POTS

POTS is a systemic syndrome which has been known for a long time under different names and is still poorly understood. Available estimates suggest that at least 150 girls and young women per million may develop POTS each year. POTS patients typically show persistent tachycardia for more than 10 minutes upon standing, as well as an increase in heart rate to above 120 bpm or by ≥ 30 bpm, and in children and juveniles below 19 years of age by ≥ 40 bpm, without arterial hypotension. A diagnosis of POTS cannot solely rely on these criteria; other symptoms (e.g. syncope, fatigue, headaches, light-headedness, diaphoresis, tremor, palpitations, exercise intolerance, near syncope upon standing upright) vary across patients and are otherwise non-specific.

In the review of clinical trial data a total of 60,594 subjects were included for Gardasil/Silgard and Gardasil 9 and 42,047 subjects for Cervarix. No cases were identified in the Cervarix and comparator cohorts. The incidence of POTS in the Gardasil/Silgard and Gardasil 9 clinical trials was less than 1 case per 10,000 person-years and comparable in the Gardasil/Silgard/Gardasil 9 and corresponding placebo cohorts.

Overall, comparisons of observed versus expected number of spontaneous reports, with the same scenarios as described above for CRPS, do not suggest an increased occurrence of POTS in relation to the HPV vaccines.

Furthermore, the detailed review of the reports did not show a consistent pattern regarding time-to-onset following vaccination or clinical characteristics.

The vast majority of POTS reports came from a centre in Denmark (Brinth et al, 2015). This centre has recently published more information on these reports, suggesting that some of these individuals were likely to have had CFS. This is in accordance with the SAG conclusions that most of the reviewed reports of POTS could better correspond to the definition of CFS or at least include some features of CFS.

A study by Donegan and colleagues (2013), using self-controlled case series design (and therefore avoiding the issue of differential diagnostic practice in vaccinated and unvaccinated), evaluated diagnoses of CFS, as well as referrals from general practice for as yet undiagnosed symptoms of chronic fatigue and exhaustion, as well as diagnoses for fibromyalgia, post viral syndrome and neurasthenia. The study found no association between HPV vaccine and any of the conditions studied.

Overall, available data do not provide support for a causal relation between HPV vaccines and POTS.

Overall conclusions

More than 80 million girls and women worldwide have now received these vaccines, and in some European countries they have been given to 90% of the age group recommended for vaccination. Use of these vaccines is expected to prevent many cases of cervical cancer and various other cancers and conditions caused by HPV.

Symptoms of CRPS and POTS may overlap with other conditions, making diagnosis difficult in both the general population and vaccinated individuals. However, available estimates suggest that in the general population around 150 girls and young women per million aged 10 to 19 years may develop CRPS each year, and at least 150 girls and young women per million may develop POTS each year. The review found no evidence that the overall rates of these syndromes in vaccinated girls were different from expected rates in these age groups, even taking into account possible underreporting. The PRAC noted that some symptoms of these syndromes may overlap with chronic fatigue syndrome (CFS, also known as myalgic encephalomyelitis or ME). The results of a large published study³⁴ showed no link between HPV vaccine and CFS. As many of the reports considered in the review have features of CFS and some patients had diagnoses of both POTS and CFS, these results were considered relevant for the current evaluation.

Taking into account the totality of the available information the PRAC concluded that the evidence does not support that HPV vaccines (Cervarix, Gardasil, Gardasil 9, Silgard) cause CRPS or POTS. The benefits of HPV vaccines continue to outweigh their risks.

The safety of these vaccines should continue to be carefully monitored. This should include follow-up of CRPS or POTS reports to determine relevant clinical characteristics, to identify possible cases of POTS and CRPS based on broad search strategies including outcome details and to compare reporting rates against available information on the known epidemiology of POTS and CRPS.

6. Grounds for the PRAC recommendation

Whereas,

- The Pharmacovigilance Risk Assessment Committee (PRAC) considered the procedure under Article 20 of Regulation (EC) No 726/2004 for HPV vaccines.
- The PRAC considered the totality of the data submitted with regard to a potential association between HPV vaccination and the occurrence of Complex regional pain syndrome (CRPS) and Postural orthostatic tachycardia syndrome (POTS). This included the responses submitted by the marketing authorisation holders, published literature, Eudravigilance data, and the outcome of the Scientific advisory group (SAG) on vaccines as well as data submitted by Member States and information submitted by the public.
- The PRAC took note of the fact that CRPS and POTS occur in the general unvaccinated population and have been described in the medical literature before HPV vaccines were introduced.
- The PRAC considered that the observed versus expected analyses took into account a wide range of scenarios regarding underreporting and included reports that did not fully meet the diagnostic criteria for the syndromes. Overall, in these analyses the rates of these syndromes in vaccinated girls were consistent with expected rates in these age groups.

³⁴ Donegan et al, (2013) Bivalent human papillomavirus vaccine and the risk of fatigue syndromes in girls in the UK. *Vaccine*; 31(43): 4961-7

- The PRAC also noted that most of the reviewed reports of POTS would more appropriately have been labelled as having features of chronic fatigue syndrome (CFS). The PRAC therefore considered the results of a large published study which showed no link between HPV vaccine and CFS, as relevant for the current review.

The Committee, having considered all the information available, concluded that the evidence does not support a causal association between HPV vaccination and CRPS and/or POTS. The PRAC confirmed that the benefit-risk balance of the HPV vaccines (Cervarix, Gardasil, Gardasil 9 and Silgard) remains favourable and recommends the maintenance of the marketing authorisations.